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Forecasting myocardial infarction and subsequent behavioural outcomes

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Abstract
Wallert, J. 2020. Forecasting myocardial infarction and subsequent behavioural outcomes. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1655. 93 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0912-5.

This thesis is compiled from four studies dealing with the prediction of myocardial infarction (MI) and some associated risk behaviours post MI.

Study 1 extends the field of possible psychosocial stress-triggering of MI to Sweden, and to the phenomenon of temporal crests and troughs in national MI rates. These findings are in the present thesis integrated into a more comprehensive theoretical framework than provided by previous studies. By controlling for different confounders, analysis in subgroups, and more, the probable effect of psychosocial stress on the triggering of MI producing slight oscillations in daily MI rates at different temporal cycles was supported.

Study 2 extends the existing literature of cognitive epidemiology to secondary preventive cardiology. Males with higher cognitive ability (CA), as assessed at mandatory military conscription in young adulthood, were found to be more adherent to their statin medication post MI, approximately 30 years later. The association is likely causal, given the fundamental importance of CA as a predictor for our individual ability to understand, plan, and execute everyday behaviour, including such health promoting behaviour as adhering to statin medication after MI.

Study 3 continues the thesis thread of predicting clinically relevant health-promoting behaviour. It generated important hypotheses of what predicts adherence to internet-based cognitive behaviour therapy (ICBT) for symptoms of anxiety and/or depression after MI. In particular, the linguistic variables which were derived from what the patients actually wrote online to their ICBT therapist, predicted adherence. Using a flexible random forest model with a moderately sized sample, the aim was to handle a range of predictors and possible higher order effects in the relative strength estimation of these predictors.

Study 4 presents the derivation and external validation of a new risk model, STOPSMOKE. Developed as a linear support vector machine with robust resampling, STOPSMOKE proved accurate in the unseen validation cohort for predicting one-year smoking abstinence at the start of cardiac rehabilitation (CR) post MI. STOPSMOKE predictions may inform the targeting of more elaborate interventions to high risk patients. Today, such intervention is not systematic as standard counselling does not account for the individual probability of future smoking abstinence failure. STOPSMOKE thus provides a novel real-world probabilistic basis for the risk of future smoking abstinence failure after MI. This basis may then be used by clinicians, patients, and organisations to tailor smoking intervention as best suited the particular individual or high-risk group. Implemented as part of a spectrum of models in a semi-automatic system, cost-effective tailored risk assessment could allow for augmented CR for future patients.

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To Mathilde, Axel, and Amelie.

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List of Papers

This thesis is based on the following papers.

I Wallert, J., Held, C., Madison, G., & Olsson, E.M.G. (2017). Temporal changes in myocardial infarction incidence rates are associated with periods of perceived psychosocial stress. A SWEDEHEART national registry study. *American Heart Journal* 191:12–20

II Wallert, J., Lissåker, C., Madison, G., Held, C., & Olsson, E.M.G. (2017). Young adulthood cognitive ability predicts statin adherence in middle-aged men after first myocardial infarction. A Swedish National Registry Study. *European Journal of Preventive Cardiology* 24(6):639-646.

III Wallert, J., Gustafson, E., Held, C., Madison, G., Norlund, F., von Essen, L., & Olsson, E.M.G. Predicting adherence to internet-delivered psychotherapy for symptoms of depression and anxiety after myocardial infarction. Machine learning insights from the U-CARE Heart trial. (2018). *Journal of Medical Internet Research* 20(10):e10754.

IV Wallert, J., Pingel, R., Schön, T.B., Olsson, E.M.G., Madison, G., Hallqvist, J., Geale, K., & Held, C. Derivation and validation of STOPSMOKE. An instrument built from Swedish population data for predicting smoking abstinence post myocardial infarction. (2019). *Submitted*.

Contents

Abbreviations

ACE	Angiotensin Converting Enzyme
AHA	American Heart Association
AM	Ante Meridiem
ARB	Angiotensin 2 Receptor Blocker
ATC	Artificial Time-Constraint
AUROC	Area Under the Receiver Operating Characteristics Curve
BMI	Body Mass Index
BPM	Beats Per Minute
C5.0	Boosted C5.0 Decision Trees/Rule sets
CA	Cognitive Ability
CABG	Coronary Artery Bypass Grafting
CART	Classification and Regression Trees
CBT	Cognitive Behaviour Therapy
CCBT	Computerised Cognitive Behaviour Therapy
CCU	Coronary Care Unit
CDR	Causes of Death Registry
CHD	Coronary Heart Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
CVD	Cardiovascular Disease
-D	Hypothesised decreased MI rates during a time period further specified relative to a control period
ESC	European Society of Cardiology
EQ-5D	European Quality of Life Five Dimensions Questionnaire
FSIQ	Full-Scale Intelligence Quotient
g	General Human Intelligence
GRACE	Global Registry of Acute Coronary Events

HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
-I	Hypothesised increased MI rates during a time period further specified relative to a control period
ICBM	International Congress of Behavioural Medicine
ICBT	Internet-based Cognitive Behaviour Therapy
INSARK	INSkrivningsARKivregistret
IQR	InterQuartile Range
IRR	Incidence Rate Ratio
ISIR	International Society for Intelligence Research
ITT	Intention-To-Treat
LDL	Low Density Lipoprotein
LR	Logistic Regression
M	Arithmetic Mean
MCR	Mandatory Conscript Registry
Md	Median
MI	Myocardial Infarction
ML	Machine Learning
mmHg	Millimetre of Mercury
mmol/L	Millimoles per Litre
N	Count
NO_2	Nitrogen Dioxide
NSTEMI	Non-ST segment Elevation Myocardial Infarction
NPV	Negative Predictive Value
OR	Odds Ratio
PCA	Principal Component Analysis
PCI	Percutaneous Coronary Intervention
PDR	Prescribed Drug Registry
PhD	Doctor of Philosophy
PID	Personal Identification Number
PM	Post Meridiem
PPV	Positive Predictive Value

Q4	The four pivotal quality goals of secondary prevention and rehabilitation for post MI patients
RCT	Randomised Controlled Trial
RF	Random Forest
RIKS-HIA	Register for Information and Knowledge on Heart Intensive Care Admissions
RR	Risk Ratio
S1-4	The four standardised scores from each of the psychometric tests from the Swedish Enlistment Battery
SBP	Systolic Blood Pressure
SCORE	Systematic COronary Risk Evaluation
SD	Standard Deviation
SEPA	Swedish Environmental Protection Agency
SEPHIA	SEcondary Prevention after Heart Intensive care Admission
SES	Socioeconomic Status
SMHI	Swedish Meteorological and Hydrological Institute
STA	Swedish Transport Agency
STOPSMOKE	STOPSMOKE risk model
STEMI	ST segment Elevation Myocardial Infarction
SVM	Support Vector Machine
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
ToP	Time-point of Prediction

1 Introduction

1.1 Causal and predictive modelling

Whether one wants to explain or predict something by means of the scientific method entails both crucial differences and similarities.[1] In the applied field of clinical medicine, the main aim of conducting a randomised controlled trial (RCT) is to estimate the causal effect of something on something else while controlling for both measured and unmeasured confounding through random exposure assignment, also aiming for neither inclusion bias nor loss to follow-up. The main question "Does X have a causal effect on Y?" is answered elegantly with the classic RCT design. If an RCT is not possible, one may still want to estimate the causal effect of something on something else. The form of explanatory modelling that is possible with the observational study design often has a high external validity albeit with the troublesome lack of control for unmeasured confounding, which potentially produces biased estimates. This is often what one has to deal with when working with real-world data gathered in an uncontrolled context without stochastic exposure assignment. The main question answered by the explanatory observational study design can be distilled to "Does it seem that X has a causal effect on Y?". Complementary to these two main approaches in which researchers around the world acquires knowledge in the life sciences, grows a third main branch of modelling which might be called pure predictive modelling. Its main purpose is to predict something, often in a future, given some other information, often gathered in the past. The main question for predictive modelling can be summarised "Can we predict Y using X?".

Differences between explanatory and predictive modelling may seem subtle yet are profound. Whereas explanatory modelling aims at distilling causal mechanisms and thus tend to view confounders as nuisance, "pure" predictive modelling can use any potential information available more freely. It can therefore ignore causality aspects of data, simply because it is not relevant to its fundamental research question. See *Figure 1* for a bird's eye conceptual view of the main modelling approaches in the present thesis.

Some scholars do not further distinguish between explanatory and causal modelling[1] but others do, suggesting the counterfactual approach as demarcation criterion and requirement for the latter.[2] The philosophy behind causal modelling has a long and rich history in Academia, dating back to Aristotle, Locke, and Hume.[3] What causality "actually is" prevails in

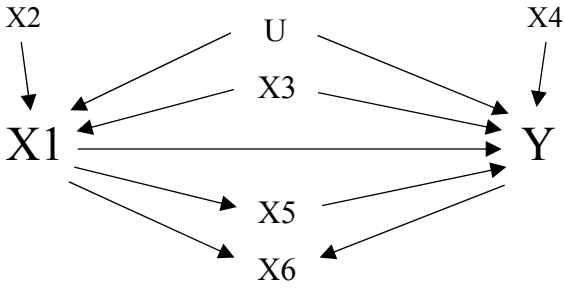
contemporary academic discussion, for instance regarding whether estimating a causal effect requires that X can be manipulated,[4] or that causal modelling does not necessarily require such a manipulability criterion.[5] A pragmatic pluralistic approach to these issues with observational data has been suggested[6] that seems more useful than both the hard-line manipulability stance in epidemiology,[7] and the even more hard-line approach of some only accepting causal explanations derived from RCTs. The pragmatic pluralistic approach also seems more in line with the core scientific values of theoretical freedom, systematic test of theory, and the inherent tentativeness of all scientific knowledge produced by imperfect human minds.

Regardless if the purpose of modelling is causal or predictive, modelling robustness is paramount. Control for overfitting is essential for all simplified versions of reality aimed at generalising to new observations. This commonality of generalisability across modelling approaches suggests that all models are predictive models. Either predicting a causal effect of exposure X1 on outcome Y or "simply" predicting outcome Y given predictors X1…Xn. The overarching purpose of both is to estimate unobservable quantities in the population from limited data. The present thesis is built around examples of explanatory and predictive modelling approaches and the case is made that both causal and predictive modelling approaches are two sides of the same quest of scientific inquiry, in finding out, with our limited senses and cognitive processing apparatus, how the world around us and ourselves within it function.

George Box once wrote that "all models are wrong but some are useful".[8] This might be the most succinct quote for capturing the human condition in its always inadequate albeit simultaneously uniquely successful quest for knowledge. Mainly through the invention, refinement, and application of the scientific method, we humans have effectively developed faster and gained more power during the most recent, tiny fraction of time compared to any other time period in our long evolutionary history.

After this theoretical bird's eye view of my thesis approach, I will now present key topics that I have spent my time learning about. These topics may seem somewhat heterogeneous, and at a superficial level, they are. However, if viewed under the umbrella theme of explanatory-predictive modelling, it should become clear to the Reader that the chosen topics interlock to serve the overarching purpose of my thesis.

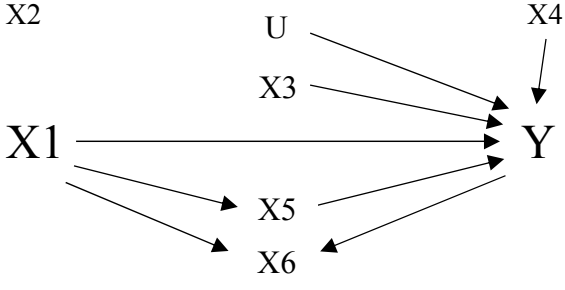
A Causal modelling – Observational study design



Estimating the effect of X1 on Y:

Unmeasured confounding, U, is impossible to directly control for. X3 is controlled to remove measured confounding. X4 is controlled to increase statistical power. X2, X5, and X6 are not controlled for since that would respectively introduce increased variance, overadjustment bias, and collider bias.

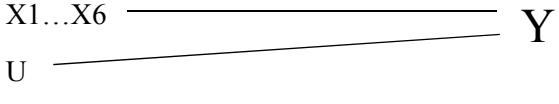
B Causal modelling – Randomised trial design



Estimating the effect of X1 on Y:

In a well-designed trial, randomisation to X1 removes edges from both measured X3 and unmeasured U confounding. This allows for unbiased estimation of the causal effect of X1 on Y. To increase power, adjustment for X3 and X4 can still be performed. X5 and X6 are left untreated as in design A.

C Predictive modelling – Risk estimation



Predicting Y given X1…X6:

X1…X6 are included regardless of eventual causality. Each X is assumed to hold potential information for Y. No particular X is emphasised as the main modelling focus is not to estimate coefficients but to optimise fit. Model fit will be imperfect to the extent of missing U. The relative predictive power of X1…X6 on Y may be particularly important.

Figure 1. **Diagrams of the three main research designs in the present thesis.** A was used for study I and II, C for III and IV, whereas B acquired data for III. The same statistical model, e.g. linear regression, can be applied for A – C, yet the result is interpreted differently. Modelling robustness is crucial across all designs.

→, Effects; ─, Associations; U, Unmeasured variables; X1…X6 and Y, Measured variables.

1.2 Data, modelling, and computing power

1.2.1 Data

Over the last few years, healthcare has begun to embrace "Big Data",[9] whatever this imprecise definition means. Although this is done hesitantly and even reluctantly in some camps, it is clear that it is having an exponential impact in medicine, including cardiology (e.g. [10, 11]). Although seemingly sudden, this development did not manifest from nothing. As usual in human affairs, it instead represents the incremental development brought about by many individuals standing on the shoulders of giants.[12, 13] I prefer to think of this development as the continuous growth of (i) data, (ii) computing power, and (iii) modelling sophistication. Psychology in healthcare has had its fair share of this development as well. Google gathers trend data on internet searches that people perform,[14] providing information on online behaviour.[15] Psychological treatments are trialled via the Internet, simultaneously also gathering log data on patient in-treatment behaviour.[16] Machines are built that learn from this and other data, for instance, which patients are likely to adhere,[17] or respond to,[18] future treatment – hopefully increasing cost- and treatment efficiency via more accurate tailoring of interventions.

1.2.2 Modelling

At the core of this development are novel applications of methods for modelling data. Machine learning (ML)[19] is now being applied at an unprecedented scale to build diagnostic and prognostic models that tend to either level with, or to some extent even surpass, human level performance.[20, 21] ML is another quite imprecise term describing the process of applying algorithms to extract meaningful information from data. This is usually done in either supervised or unsupervised form.[19] Supervised when the algorithm is provided a target with the objective to predict this target,[22] and unsupervised when no target is fed to the algorithm and the objective is to find out how data clusters with no specified modelling target.[23] A model trained on a number of labelled cases for estimating the probability for survival vs non-survival two years after first cardio-specific event exemplifies supervised learning.[24] Cluster analysis modelling for identifying how many distinct clinical types of procrastinators exist, i.e. not labelled beforehand, is an example of unsupervised learning.[25] For unsupervised learning, the machine functions to a greater extent as the teacher, as it more independently learns patterns in data that are potentially useful for explaining or predicting something. Roughly since 2006,[26] more complex machines called deep neural networks, have achieved exceptional success and notability with high-dimensional data, employing crude imitations of the layered processing-style of the mammalian neocortex to achieve unprecedented performance on several advanced

problems of speech recognition and image processing.[27] Great future progress is also expected, as researchers construct more accurate algorithms that mimic human learning and decision-making.[28] As with electricity, ML is now seeing effective application within a range of human fields of expertise (e.g. automotive industry, capital investment, speech translation, image recognition) and decision support systems for healthcare diagnostics and prognostics are being developed (e.g. *Figure 2*).

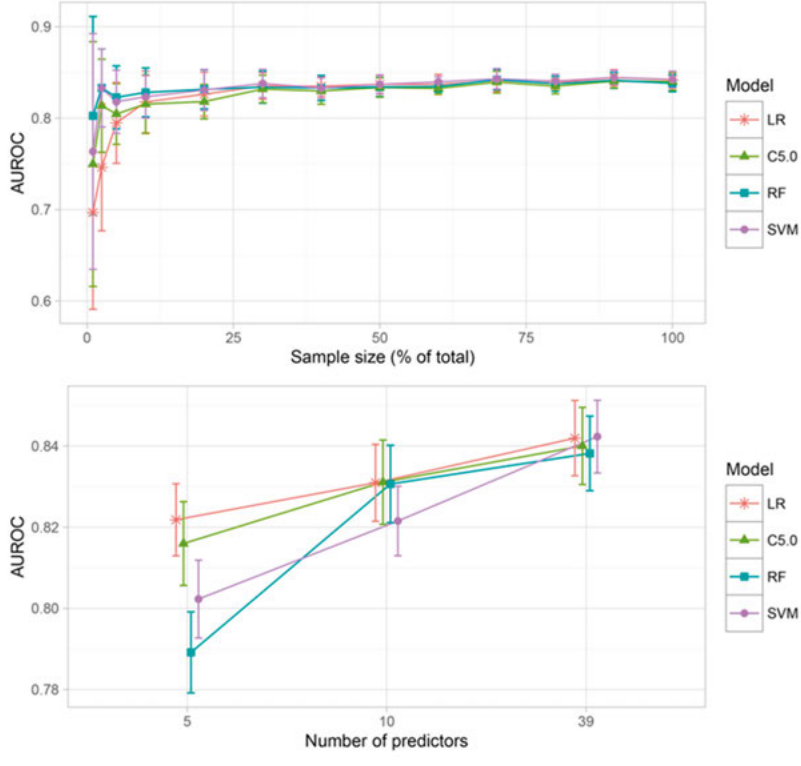


Figure 2. **Example of solving the binary prediction problem of differentiating survivors from non-survivors two years after first-time MI by training four machine learning algorithms on SWEDEHEART acute MI data.** Top: Model training performance as a function of increased sample size (1 – 100%). Bottom: Model training performance on three different predictor sets using 100% of training samples. Points are mean values of each model's resampled training runs with 3x7 repeats of cross-validation, tuned over the performance metric Area Under the Receiver Operating Characteristic (AUROC). Error bars indicate ± 1 SD. C5.0, Boosted C5.0 Decision Trees; LR, Logistic regression; RF, Random Forest; SVM, Support Vector Machine. N patients = 31,166. (Wallert et al, 2017, *BMC Med Inform Decis Mak*[24])

1.2.3 Computing power

Building complex models using rich data is computationally expensive. Breakthroughs in computation on both distributed[29] and local[30] high-performance systems now paves the way for both data collection and modelling in a previously unprecedented fashion. Before 1970's, fitting an ordinary least squares model to moderately sized data could take up to 24 hours to finish. Today, it is possible to run a more complex extension of that model[31] in a contemporary open-source statistical program[32] on a standard portable computer with orders of magnitude of more data and receive the result within seconds *(Figure 3)*. It seems appropriate to emphasize that at this point in time, compared to all preceding time-points in our species evolution on this planet, has there never existed such a technological grounding for new knowledge to be gained.

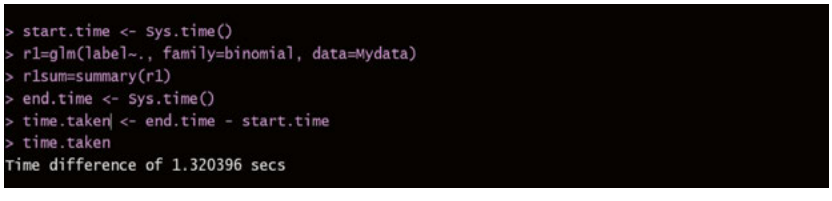


Figure 3. **Contemporary computing power.** The time it takes to run a binomial logistic regression with 51,943 MI patients with complete values on 40 variables in R on the author's present laptop computer. All maximum likelihood point estimates, standard errors, z-values, p-values, input data, and more are stored in the object "r1sum". The whole model, "r1", has the size of 60.5 Megabytes.

1.3 Cardiovascular disease

1.3.1 Myocardial infarction

Myocardial Infarction (MI) is the most common acute event of underlying Coronary Heart Disease (CHD) – the leading cause of death in the world. Around 7 million humans worldwide suffer an MI each year.[33, 34] The European Union (EU) costs in 2009 related to cardiovascular disease amounted to 106 Billion EURO, roughly 9% of the total healthcare costs.[35]

In Sweden, there were more than 150,000 MIs registered at Coronary Care Units (CCU) from 2006 through 2013, amounting to an average of more than 18,750 registered MIs per year registered at CCUs in Sweden with an average of 51.8 MIs per day with a mean age of 71.8 years at hospital admission. More than two thirds of these MIs were first-time MIs. Acute care has seen a phenomenal improvement over the last 15-20 years during which the mortality rate has decreased by about 50%.[36] The reasons for the increased survival rate across time is the result of improved healthcare,[35] both with respect to diagnostics, treatment and care,[37] and technological development (e.g. [38, 39]).

CHD is often developed over decades as a function of both lifestyle factors and genetics,[35] for which smoking, diabetes mellitus, physical activity, socioeconomic status (SES), and other supposedly modifiable lifestyle risk factors explain most of the MI risk.[40] The acute outcome of MI has been suggested as triggered by a plethora of quite different factors, including earthquakes,[41] sporting events,[42] slight alterations of the societal time-keeping [35],[43] outbursts of anger,[44] sexual activity,[45] shift work,[46] psychosocial stress[40] and temporal fluctuations in psychosocial stress (*Figure 4*, and [15, 47]).

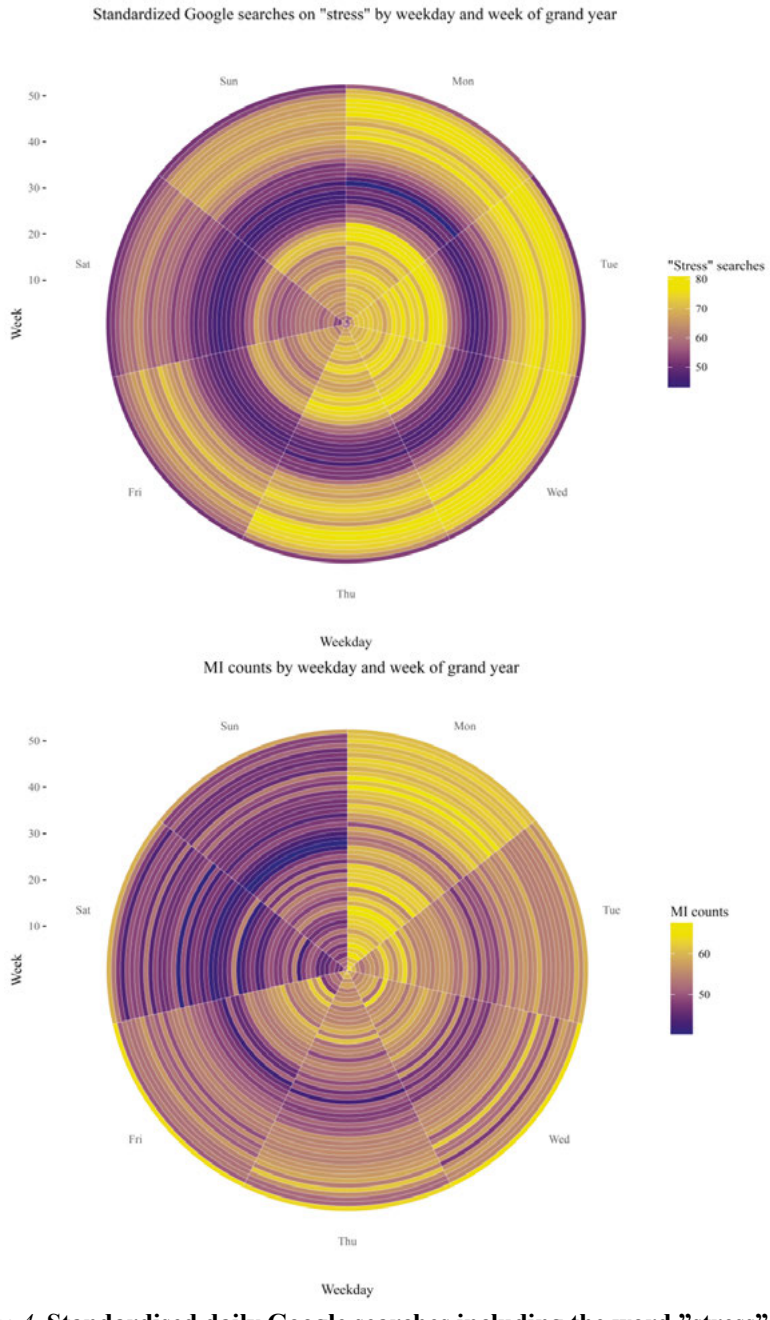


Figure 4. **Standardised daily Google searches including the word ”stress” and the corresponding daily myocardial infarction (MI) count aggregated per weekday (cake slices) and week of the year (growth rings) across years 2006-2013**. Spearman’s rank-correlation coefficient (rho) between the two variables is ρ = .53, p < .001. N cases of MI = 156,066. (Wallert, Poster presentation, International Congress of Behavioural Medicine, ICBM, Melbourne, Australia[15])

1.3.2 Risk factors

A risk factor is a variable related to a negative outcome, most often a disease or a disease-related adverse event, with an assumed a causal link.

A risk factor can be *somatic*, e.g. diabetes as a factor for attending exercise training after an MI,[48] *socioeconomic* if the risk factor is highest attained education or disposable income on subsequent cardiac events,[49] *behavioural* when considering attending patient education post MI on the risk of future mortality,[50] or even *biopsychosocial* whereas "stress" seems to trigger MI.[42, 44, 47] A risk factor can manifest fairly quickly (statin non-adherence), gradually over time (hypertension), and it can also prevail consistently (cognitive ability) or fluctuate (recurring depression) over decades.

Granted that a risk factor typically predicts an adverse hard-endpoint event, for instance mortality, MI, or stroke, but the range of outcomes may also encompass clinically relevant behavioural outcomes, such as smoking cessation failure, medication non-adherence, damaging alcohol consumption, or sleep disturbances.

The risk factor palette for patients with CVD is substantially behavioural. Yusuf and colleagues have found that a lion's share of the population attributable risk (PAR) is due to modifiable risk factors.[40] Several risk factors are thus considered to be alterable through conscious effort,[51] as opposed to being predicated on behavioural genetic make-up and then phenotypically expressed fairly consistently, in large part irrespectively of the environment or personal voluntary action.[52] Consensus guidelines for secondary prevention consistently emphasise the need for behavioural change to reduce the post MI risk.[51] Meanwhile, it is clear that even in the relatively rich and well-developed region of the EU, secondary prevention holds room for considerable improvement.[53]

How to exactly achieve such behavioural change is less clear than the repeatedly voiced need for such an achievement. Both nature and nurture are at play regarding behavioural change in humans.[54, 55] It is therefore likely that both behavioural medicine and behavioural genetics could enrich each other and the knowledge output back to society from such a combinatory effort. In particular, a pragmatic approach to improved health-promoting behavioural change in patients with CVD would benefit from discerning to what extent risk behaviours are malleable, and to what extent they are not.

1.3.3 Secondary prevention

In contemporary western societies, relatively few die from suffering an MI.[37] For instance, two years after their first MI hospital admission in Sweden, only ~14% of patients are deceased.[24] As acute MI care has improved markedly over the last few decades, more surviving patients automatically end up in need of secondary prevention after MI. As restated, such secondary preventive

cardiac rehabilitation (CR) holds room for improvement.[36, 51, 56, 57] Idiosyncratic patient behaviour during secondary prevention is crucial for lowering the reinfarction and mortality risk, and hence entails another layer of complexity compared to the quite brief acute care stage, wherein the patient's own behaviour has limited or no influence on acute outcomes. Naturally, health promoting behaviour is of course crucial before suffering an MI. Primary prevention is however not the focus of the present thesis, but rather on secondary prevention. According to the 2016 SWEDEHEART report on secondary prevention, only 21% of patients achieved the four most important CR goals (Q4), including smoking abstinence, participation in a physical activity programme, lowered systolic blood pressure (SBP) < 140/90 mmHg, and reduced low-density lipoprotein (LDL) to < 1.8 mmol/L or reduced by 50%.[58] There is also a substantial variation between Swedish hospitals regarding Q4 patient fulfilment, where the best achieve 40% fulfilment, which has been stated explicitly as the target goal for all hospitals in Sweden.[58] Naturally, the Q4 goals are to some extent directly related to patient behaviour,[48, 50, 59] and otherwise also indirectly related to patient behaviour such as non-adherence to lipid lowering medication.[60-63]

1.3.4 Possible paths towards augmented patient health

From the clinical psychologist's perspective, there seems to be a behaviour-specific need for improving secondary preventive cardiology. Because behavioural change is critical for the patient risk after MI, experts on behavioural change may be needed to improve secondary prevention. Possible paths towards improvement include (a) a deepened understanding and improved prediction of psychological aspects of the human stress response and its possible relation to triggering of MI [15, 41-43, 46, 47], (b) improved understanding of early-in-life cognitive determinants for later-in-life risk behaviour and behaviour-related outcomes post MI [59, 60, 64], and (c) identifying new predictors in data-driven approaches to develop accurate predictive models for post MI patients,[17, 65] possibly particularly for predicting risk behaviour during secondary prevention.

1.3.5 Prediction for improving patient health

Regarding pure prediction, there are specific application possibilities. For instance, the hospital discharge date is the specific time-point when patient monitoring decreases dramatically, and the need for improved predictive modelling of behavioural risk factors and hard endpoints increases correspondingly. This is also the time point for when we lack solid predictive models, as compared to hospital intake predictive models (e.g. [66]). Since only about 1 in 5 of post MI patients fulfil their Q4 goals one year after their MI, and because fulfilment rate varies considerably between hospitals,[36, 57] efforts

to further advance secondary preventive care has considerable potential.[51] In the United Kingdom alone, a reduction in population cardiovascular risk by only 1% would translate into 25,000 fewer MIs and save 40 million EUR annually.[35] Of course, post MI patients constitute a subpopulation of these, but healthcare expenditure for patients after MI is nevertheless substantial with more than 70 new MIs registered per day in Sweden alone. The cost of CR follow-up after suffering an MI is substantial, often entailing a range of physiological measurements, revisits to both the cardiologist and cardiac nurse, different health promoting programmes, and including referral to other healthcare professionals (e.g. psychologist, dietician, physiotherapist, et cetera). In addition, work absenteeism costs for patients, and/or their significant others, travelling costs, and the cost for facilities should be mentioned. If we could predict the range of risk behaviours together with risk for hard endpoint outcomes, we might be able to target the resulting risk groups in need of more frequent and less frequent follow-up. This should in turn improve both healthcare expenditure and patient-tailored care.

For post MI patients that also suffer from symptoms of depression or anxiety,[61, 62, 67] prediction models that estimate a new patient's probability for adherence to, and also treatment effect of, psychotherapy should be useful (see [18] for a similar reasoning and for the target psychotherapy RCT[16] which generated data for Study III). Around 20% of MI patients suffer from clinical depression, indicating higher prevalence than in the general population[68] and depression is associated with poor prognosis[69] and a higher risk factor burden (e.g. [70]). Psycho-affective pathology is also a concern in other CVD patient subgroups.[71] However, it is unclear if screening for or treating depression has a causal effect on cardiac outcomes.[16, 72] Anxious and depressive symptomatology is however associated with CHD and mortality.[62, 73] This was the rationale for the U-CARE Heart trial, which evaluated the effect of a tailored psychotherapy programme for comorbid anxiety or depression symptoms in post MI patients.[16] In U-CARE Heart, licensed psychologists and patients performed cognitive behaviour therapy (CBT) over the Internet (ICBT) with minor telephone support. Recruitment at > 20 CCUs across Sweden also provides a novel opportunity to evaluate ICBT for these patients in terms of stronger external and ecological validity than usual for psychotherapy RCTs. Although an empirical question, the predictive model in Study III should – because of the recruitment procedure and coverage of U-CARE Heart – generalise relatively well to new post MI patients suffering from anxiety or depression.

In general, implementation of predictive models require close interaction with clinicians. Predictive models as decision support may help clinicians with key parts of tailored care. For instance, patients predicted to have high risk for discontinuing their statin treatment, or with a high risk for continuing smoking, may benefit from tailored monitoring based on their predicted risk of discontinuation/failure. Regarding psychologically frail patients we should

be extra careful to offer interventions if the risk for non-adherence or non-effect/negative effect is too high. If we could at the start of treatment predict patients with high-risk for non-adherence to a treatment, we could then use that information to limit inefficient treatment, or replace it with more efficient treatment.

1.4 National registries

1.4.1 Overview

With its Scandinavian neighbours, Sweden shares the fairly unique situation of maintaining annually updated national registries with excellent population coverage and data quality. In the healthcare sector, more than 100 registries for different diseases are maintained under regulation by Swedish law. This national framework makes it possible to both (a) continuously monitor and improve Swedish healthcare, and (b) to conduct registry-based research in our country. Through the use of the personal identification number (PID), linkage with other specified registries is possible, for instance the Causes of Death registry (CDR) and Prescribed Drug Registry (PDR) through a fairly standardised procedure performed by the National Board of Health and Welfare. Together with the high quality of data collection and monitoring and the statistical power with population data, the main strength of the top-tier of these registries is that they are unselected. This means that an opt-out procedure with passive informed consent is employed.[36] Had these registries used patient opt-in with informed consent as formulated in the newer version of Declaration for Helsinki,[74] for instance, their main strength would have been destroyed due to selection bias. Today, each patient is informed of their inclusion and their right at any time without need of further disclosure to have their data erased from the registry. Extremely few patients require exclusion. To summarise, Swedish registries represent a unique combination for consistently improving healthcare by means of both clinical quality control and clinical large-scale research in a cost-effective manner.[36, 58, 75-77]

One limitation with these kinds of registries is that the variables measured are already decided, sometimes long ago. Often these variables are sufficiently good, both in terms of the amount and breadth of their combination, with considerable care and expertise invested in deciding on what should be registered. Sometimes however, the choice is suboptimal, leaving the researcher with only a proxy of the variable one would want to study. Changing registry variables is slow process, which is both good and bad. Good, because it assures stability in the system and temporal consistency in measurements is often highly regarded by researchers aggregating several years of data, and crucial for repeated measures designs. The downside of this is that these registries are not the fastest in implementing new and improved

measurements. Overall, the greatest strength of these registries for research is displayed when combining several of them together, allowing for rare combinations of data with which important explanatory and predictive research questions can be answered.

1.4.2 SWEDEHEART

The Swedish Web-System for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) is the only complete national quality registry on CVD in the world. With its excellent coverage, random and continuous monitoring, clinically integrated data collection, and digital reporting of highly standardised and comprehensive data down to the individual site level in annual reports, SWEDEHEART provides both a solid structure for continuous improvement of healthcare and unique possibilities for conducting research from the early acute care through to the end of secondary prevention. The Swedish Board of Health and Welfare ranks SWEDEHEART in the absolute top-tier of the +100 national quality healthcare registries in Sweden.[58]

Under its umbrella, SWEDEHEART accommodates several registries[36] maintained by the Uppsala Clinical Research Center. The Register for Information and Knowledge on Heart Intensive Care Admissions (RIKS-HIA) is the oldest and largest of the SWEDEHEART sub-registries, collecting more than 100 variables on medical history, symptom onset, hospital admission, comorbid conditions, biomarkers, behavioural risk factors, acute triage and treatment interventions, Electrocardiogram (ECG), discharge medications, and more. RIKS-HIA seeks to include all Swedish patients admitted for acute coronary syndrome, and includes patients from all CCUs in Sweden with excellent national coverage (> 90% of all MIs < 80 years of age). RIKS-HIA form the clinical population basis for Study I, II, and, IV with which other registries were merged. The registry for Secondary Prevention after Heart Intensive Care Admission (SEPHIA) is the second largest of SWEDEHEARTs sub-registries and collects data at two time-points, 6-10 weeks (SEPHIA1) and 12-14 months (SEPHIA2) after the MI, on more than 40 variables with a comprehensive focus on lifestyle risk factors, partaking in cardiac rehabilitative interventions, self-assessed quality of life, mobility, and emotional distress. SEPHIA aims to include all Swedish patients referred to secondary prevention. Patients from 97% of Swedish CCUs are registered in SEPHIA with very good national coverage (> 80% of all post first-MI patients < 75 years of age).

Combining data from RIKS-HIA and SEPHIA provides a solid foundation for conducting research within the behavioural cardiology field. One could make the case that these annually updated registries constitute “Big data” of very high quality. Because we discuss unselected population data, findings are highly generalizable to the Swedish MI population under study, and the

ecological validity with real-world data of this kind is very high. Registry data provides the necessary statistical power for conducting research with extensive control for nuisance variables and achieve high precision in estimates. With > 100,000 unique cases of MI registered during the last decade, there is also the possibility of studying rare exposures, outcomes, and subpopulations of patients. From a pure predictive modelling perspective, data also provides particularly good possibilities for building very robust and accurate predictive models. The superior generalisability due to these registries unselected coverage and real-world quality, and the registry-apparatus already in place, actual implementation of predictive models as decision support in routine care is likely to be particularly straightforward.

1.4.3 INSARK

The Swedish Mandatory Conscript Registry has been heavily used in research, including cardiovascular epidemiology,[78] cognitive epidemiology,[79] and psychometric thesis work,[80] for example. According to the Swedish National Archives,[81] a particular version of this registry covering the conscripting years of 1969 to 1997 have been digitised for its high quality. This database goes by the name Inskrivningsarkivregistret (INSARK) and was used for the present work via linkage with the SWEDEHEART registries and more. The present route was primarily to advance research on cognitive epidemiology within the specific realm of what one might call "cognitive cardiac epidemiology". Registry linkage of SWEDEHEART with INSARK while focusing on secondary prevention post MI, provides a new opportunity for cognitive epidemiology research questions.

1.4.4 Additional registries

Data linkage with other high-quality registries was necessary for some of the studies in this thesis. The PDR is maintained by the Swedish National Board of Health and Welfare and registers all outtakes of drugs from pharmacies in the country. Dispensation date, prescription date, dosages and more are either directly available or can be calculated with data from the PDR.[82]

Statistics Sweden maintains the Swedish Total Population Registry (Registret över totalbefolkningen) and interlinked sub-registries which annually updates data for all Swedish citizens on their highest attained education, different measurements of income, country of birth, marital status, and more.[83]

Other registry-type sources were used, although more sparingly: The CDR for time and underlying cause of death, the Swedish Meteorological and Hydrological Institute (SMHI) for daily temperature data at weather stations closest to hospitals with MIs registered in SWEDEHEART, the Swedish Environmental Protection Agency (SEPA) for corresponding air pollution

data, and the Swedish Transport Agency (STA) for data from all Swedish airports on monthly travelling in and out of Sweden.

1.5 Thesis-specific risk factors and outcomes

1.5.1 Stress

This complex biopsychosocial phenomenon may trigger CVD events, including MI.[41, 42] Stressors in daily life are in turn related to the risk of MI across sex, age, ethnicity, and nationality.[84] The prevailing conceptual model of stress, the job-strain model, postulates that low personal control paired with high demand in one's work environment leads to "mental strain",[85] which is associated with increased risk of MI.[86, 87]

The incidence of MI exhibits temporal fluctuation. Variation in CVD incidence rates across time in a population is not entirely stochastic but in part systematic. During the Christmas and New Year holidays there is a distinct peak in incidence rates.[88, 89] The beginning of the month,[90] week,[91] and day[92] also display a higher average incidence rate. These time periods tend to coincide with periods of modern life that are subjectively stressful, e.g. preparing for Christmas, paying monthly bills, returning to work on Monday, and morning transport to work. In contrast, weekends and the month of July have shown a nadir in MI rates relative to other weekdays and other months, respectively.[93, 94]

There is only partial alignment of these periods with our internal time-keeping. This biological clock, the circadian system, is hardwired in our genes, and its origin traces back through millions of years of evolution, as an adaptation to the smooth changes in the diurnal light-dark cycle on Earth.[95] To some extent, contemporary life in developed countries thus poses a challenge to our innate biological clock, through its ubiquitous use of artificial light, and arbitrary timed behavioural requirements (shift-work, Monday mornings, or nightly Christmas preparations).

Previous research corroborates this misalignment by showing that even minor manipulations of sociocultural time-keeping is associated with elevated MI rates in spring during the following week from when one hour is subtracted for daylight saving but not in the fall when the hour is added back.[43] Findings from psychoneuroendocrinology also show a higher morning peak cortisol during weekdays compared to weekends and self-rated stress was corroboratively higher during weekdays relative to weekends.[96]

Taken together, the aforementioned findings suggest that (i) different types of stressors, (ii) in different contexts, (iii) across different lengths of time may lead to similar increases in MI risk. This implicitly also suggests some MI-relevant commonality shared by these stressors, in these contexts, during these timespans.

1.5.1.1 The Artificial Time-Constraint Model

To better understand the cyclic nature of MI rates over time and their possible relation to stress, I herein propose an Artificial Time-Constraint (ATC) conceptual model, which has been further refined supported by my supervisors. The ATC model describes the human stress response to the extent that it is conditioned on the often arbitrary rules of modern society imposed on the individual – in part misaligned with our innate biological clockwork and sensory capacity. The term "Artificial" is chosen because the human stress response is well-adapted to stressors that have existed for millions of years, yet struggles notably when exposed to evolutionarily novel stressors in modern society, as previously exemplified. "Time-Constraint" in singular is used to emphasize that it is one concept quite different from the commonly used "time-constraints".

The concept ATC represents the degree of temporal deviation from being able to comfortably perform adequate behaviour within a context. This contrasts the ATC model with the established job-strain stress model suggested by Karasek,[85] which is not applicable to temporal fluctuations in MI rates because the job-strain model (a) ignores the temporality of stress, and (b) is limited to a work context. ATC is evident within the realm of work (e.g. deadlines, 9-5 work) but also in situations not directly related to work (e.g. the holidays). The ATC model therefore complements the job-strain model with an integrated perspective on stress and stress outcomes by collapsing demand, control, and time into the single concept of ATC.

Through the intermediary of psychosocial stress, the degree of ATC can then be used to predict variation in stress-sensitive somatic outcomes, such as MI incidence rates. Or phrased differently, [ATC → stress response → triggering of MI] is suggested to vary in intensity in partial unison across time. This is valid because (a) perceived stress is intrinsically dependent upon the amount of available time one has for producing adequate behaviour, (b) available time fluctuates systematically with arbitrary time-keeping in society (e.g. shift work, Holidays, summer vacation, and the work week), (c) this arbitrary time-keeping is partially misaligned with our innate, biological time-keeping, (d) excessive stress will arise in the organism due to this misalignment, and (e) this excessive stress is likely to impact on MI rates. Since this excessive stress varies over time, MI rates should vary correspondingly. The ATC model offers a first attempt to combine previously known stress-sensitive cardiovascular event fluctuations – such as MI rates – within a single theoretical and predictive framework. See *Figure 5* for a graphical image of the ATC model and its predictions.

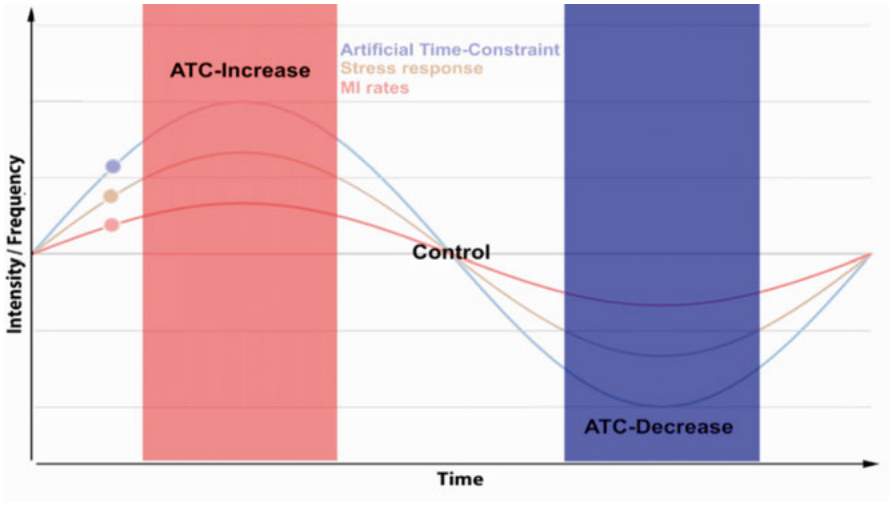


Figure 5. **Conceptual plot of the study hypotheses and ATC theoretical framework.** Notice the remaining control days in light grey after defining both periods expected to have particularly high MI rates in red (ATC-Increase), and periods of particularly low MI rates in blue (ATC-Decrease). In order from greatest to smallest amplitude over time, the three sinusoids represents (a) the intensity of ATC in the Swedish society, (b) the resulting intensity of the human stress response, and (c) the predicted frequency fluctuations in daily MI rates. This image is captured from a moving image sequence. ATC, Artificial Time-Constraint; MI, myocardial infarction (Wallert, Oral presentation, European Society of Cardiology Congress, ESC, Rome, Italy, 26-31 August, 2016).

1.5.1.2 The ATC model rationale and predictions

The ATC model predicts both periods of high and low ATC (and high and low somatic event rates per unit time) which can then be tested versus the remaining control days during which an "average" level of ATC is present (and average somatic event rates are expected). This contrasts with previous research that focuses on comparing increase versus control periods for CVD events (e.g. [42, 90]). The ATC model predicts *ATC increases* during (i) Mondays when the workweek starts, (ii) the turn of the month due to financial and/or administrative deadlines, and (iii) the turn of the year coinciding with family gatherings during the winter holidays. Correspondingly, *ATC decreases* are predicted during (iv) weekends and (v) in July as it coincides with the bulk of 4-6 weeks paid summer vacation in Sweden. Since Swedes spend most of their annual vacation in July,[97] an all-month trough in MI rates is predicted during July versus the remaining 11 months. In July, we are arguably the farthest away from ATC during the entire year. Likewise, the weekend is the least time-constrained period of the week and therefore the model predicts that weekends have the lowest weekly MI rates. The ATC model also predicts that the Monday increase in MI rates would be more pronounced in the working

relative to the non-working population. Simply because workers have relatively more ATC exposure on Mondays compared to those not required to go to work that day. Naturally, societies with different holiday periods or work norms will have different patterns of ATC and the ATC model predicts MI rates corresponding to those periods instead.

One way to test the ATC model would be to measure objective stress markers over time in the population and relate them to MI rates. Another would imply gathering questionnaire data on perceived stress and relate their aggregate to the time-periods suggested by the ATC model. Both ways would require substantial resources to merely sample the MI population. The present approach was to let previous research on temporal MI surges and population-wide cultural knowledge on subjective stress and relaxation guide the choice of what time periods should be defined as ATC increases and ATC decreases and relate them to national registry data on actual population MI rates.

We see that the theoretical framework of the ATC model provides several specific and therefore testable hypotheses, continuing the post-positivism tradition of conjecture and refutation as championed by Karl Popper[98] and further developed by others.[99] In other words, we construct theory that suggests to explain the world, thereafter we test our theory trying our best to falsify it, and in light of empirical results we either validate, refine, or discard our theory. We then tentatively put our faith in the theory of highest verisimilitude. We collect data so that we can pose questions to data, and explanatory modelling is of limited use and prone to post-hoc bias without guidance by preceding theory. The ATC theoretical model is therefore superior to an agnostic empirical assessment of data followed by post-hoc reasoning about the possible causes of these fluctuations in MI rates across time.

1.5.2 Cognitive ability

One of the oldest and most extensively researched phenomena in the history of psychology is intelligence, also called cognitive ability (CA). CA signifies the aggregated intellectual capacity of an individual.[100, 101] This capacity can be further subspecified in more or less distinct cognitive capacities such as information processing, memory, and executive function.[102, 103] Studies employing factor analysis or other dimension-reduction techniques to uncover latent variables from a group of human responses on a set of psychometric tests tend to find that the first factor/principal component explains 50% or more of the variance in test scores from different psychometric tests,[59, 60, 104, 105] with general intelligence at the top in a tri-hierarchical factor model usually providing the best fit.[106] To simplify, the performance on different psychometric tests is positively correlated, no matter what type of test is administered. Spearman dubbed this phenomenon the positive manifold,

which laid the foundation for the theory of general intelligence, psychometric *g*, more than a century ago.[100, 101, 107, 108]

Clinically widespread theoretical variants of human cognition have since then been constructed around consistent empirical findings of this general factor of human intelligence (e.g. [103, 109]). Genetic and hereditary studies have shown that this CA factor is heritable,[52, 110] according to a meta-analysis from 2015.[54] This is likely a rather low estimate since different tests of CA because varying *g* loadings of many tests were aggregated. Another study suggests 82%.[106] After puberty, CA has largely fixated and inter-individual differences show very high stability over 18-65 years of age.[104] Another important aspect is that the heritability of CA increases with age,[52] which is not contradictory to a person's standing on the *g* factor being very stable across most of that person's adult lifespan.

A first step of operationalising latent CA for use in research is through psychometric testing. Preferably, several tests are used, tapping different but interrelated narrower mental abilities, each with sufficient *g* saturation (substantial factor loadings on *g*). Their aggregate score can then be considered the Full-Scale Intelligence Quotient (FSIQ) standardised to some scale, usually the Standard scale of population mean (M) = 100 and standard deviation (SD) = 15. Other popular scales with which to represent CA include the T-score (M = 50, SD = 10), and Stanine (M = 5, SD = 2). Moreover, CA has a known Gaussian distribution, similar to how height and weight are distributed in the human population. This means that the relative frequency of individuals in the population with particular CA scores can be calculated.

1.5.2.1 Predictive validity

CA has long-term predictive validity for a range of important life outcomes, including the three key socioeconomic status (SES) markers of educational attainment,[111, 112] job status and performance,[101, 113, 114] and income.[112] Across the life-span – and particularly in brain formation years in the young – there also seems to be an intricate interplay between CA and socioeconomic factors.[111] To exemplify with educational attainment, performance on the well-known Scholastic Aptitude Test (SAT) is correlated with CA at .82.[115] Hence, the SAT is effectively a test of CA. Furthermore, in a population-representative study of +70,000 children at age 11 using several psychometric tests and several educational achievement scores, the correlation of latent CA and latent educational achievement is .81.[116] The aforementioned should be kept close in mind when to discuss, analyse, and interpretation of SES should be done in conjunction with CA, for instance with respect to risk factors for disease outcomes. CA and SES may very well be two separate operationalisations of the same underlying phenomenon (*Figure 6*).

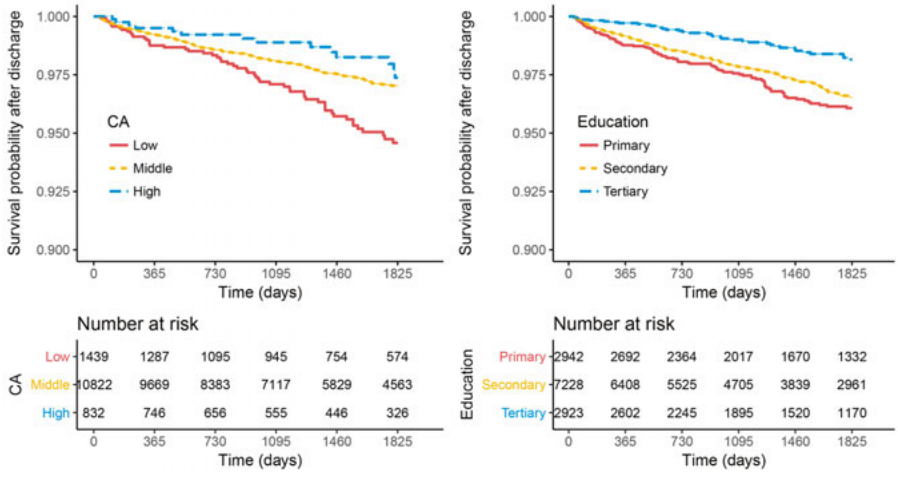


Figure 6. **The same latent variable in effect?** Survival curves with risk tables for five-year all-cause mortality in first-time MI male patients by levels of CA and Education, respectively. CA, Cognitive ability. N = 13,093. (Wallert, Poster presentation, International Society for Intelligence Research, ISIR, Annual Conference, Edinburgh, Scotland[117]).

The field of cognitive epidemiology has mapped the broad predictive power of CA for several outcomes and behaviours related either directly or indirectly to cardiovascular disease. It has been found that a person with higher CA is more likely to (i) be physically active,[118] (ii) eat healthier food,[118] (iii) possess higher health literacy,[113] (iv) be a non-smoker,[119] (v) not have hypertension,[120] (vi) not develop CHD,[121] and (vii) live longer.[122] To continue along this research path, narrowing in on CVD post MI in particular seems both logical and important.

Although we cannot directly manipulate CA without overstepping ethical boundaries, it might be possible to tailor the healthcare of individuals to better suit their CA.[59, 60] There are several examples from both the education of our young, and the geriatric care of our old, where interventions and the environment are in part tailored to the cognitive capacity of the pupil and patient. In secondary preventive cardiology, CA tailoring of, for instance, the patient communication remains largely unchartered territory and thus constitutes a possibility for more-effective tailored care. After an MI, the patients' own behaviour is instrumental in succeeding with behavioural changes to influence their risk of reinfarction or premature death, and CA seems to be broadly predictive in terms of how well these patients succeed.

1.5.2.2 Lack of Acknowledgement

Despite the aforementioned bulk of evidence of both long-term, stable predictive power and plausible causal links from CA to a range of risk factors and hard endpoints, it is surprising that CA is not mentioned in consensus cardiology guidelines.[35, 51] There are brief instructions regarding the treatment

and care of elderly suffering from dementia-related cognitive decline, but this is very different from CA. The lack of CA in guidelines becomes even more surprising when these guidelines acknowledge several factors that are themselves determined to a substantial extent by CA (e.g. SES).

1.5.3 Statin adherence

Elevated blood lipids/LDL-cholesterol is one of the most important risk factors for MI with a population attributable risk of 50% worldwide.[40] Appropriate statin treatment and adherence is effective in reducing blood lipid levels, which leads to reduced post-MI mortality by up to 25%.[123] Almost all first MI patients are prescribed statins today, yet only around 70-80% are adherent to the medication when defined as dispensed outtake of 80% of the prescribed annual dosage over a year.[124] There are also in part difficult public attitudes related to adherence to medication, possibly due to antipathy towards the pharmacotherapy industry.[125] Non-adherence to cardiovascular medication is a complex, multifactorial problem, associated with symptom and disease severity, side-effects severity, health literacy, socioeconomic factors, and personality.[63] There is still incomplete knowledge regarding what factors influences statin medication adherence – knowledge that, if gained, could augment tailored interventions aimed at improving statin adherence.

1.5.4 ICBT for MI-ANXDEP

A large subgroup of patients with MI are also burdened by symptoms of anxiety, depression, or a combination of the two (MI-ANXDEP). MI-ANXDEP stand out from the large group of MI patients as MI-ANXDEP are encumbered by a higher risk burden.[73, 126] Additional rehabilitation for MI-ANXDEP thus involves psychological treatment/support[127-129] targeting psycho-affective symptoms and thereby possibly also encouraging healthy behavioural change leading to reduced CV risk.[35, 51]

Among the plethora of psychological interventions available, cognitive behaviour therapy (CBT) and internet-administered adaptations of CBT (ICBT) have shown effectiveness at reducing hallmark symptoms for most common psychiatric disorders.[130, 131] Arguably an effective treatment for some patients, ICBT often has substantial non-adherence, although a bit lower if ICBT is manually supported by a treating clinician rather than supported by a less skilled administrator. Meta-analysis estimates of dropout in such guided intervention trials for depression has been estimated to 28% with manual skilled support, 38% for manual unskilled support, and 74% if unguided, with a total dropout of 57% over the 40 included studies.[132] In a systematic review of computerised CBT (CCBT), the median treatment completion of CCBT trial participants was 56%.[133] With ICBT, there are also specific technological demands on the online machinery and the operation of this machinery, which

is not always up to date.[134] Even before taking into account general ICBT study limitations, including technological demands on the patient coupled with the often narrow inclusion criteria in ICBT studies, and that ICBT does not allow for blinding to treatment, non-adherence to treatment justifies intensified research into ICBT adherence.[135] From the very nature of ICBT and its voluntary and behavioural-altering core of treatment mechanics, it follows that adherence to ICBT is a prerequisite for having even a possible effect from ICBT.

The U-CARE Heart trial was the first and remains the largest to date multi-site RCT targeting symptoms of anxiety and depression in MI-ANXDEP with therapist-supported ICBT compared to treatment as usual (TAU).[16] The trial design benefitted from high ecological validity through broad, clinical routine recruitment[136] relative to other ICBT trials recruiting via self-referral and applying more narrow inclusion criteria.[133, 137] The primary intention-to-treat (ITT) result of U-CARE was a null effect of ICBT, probably in part due to low adherence. The trial result underscores the need to investigate the practical effect of ICBT under ecologically valid conditions,[138] and if non-adherence hampers the effect, predictors for adherence need to be further investigated.

Similar to medication adherence, ICBT adherence seems predicated on multiple factors.[135] Predictors for ICBT effectiveness and/or adherence also show substantial overlap across clinical subgroups, with previous studies identifying pre-treatment symptomatology, older age, female sex, high motivation, face validity (treatment credibility), therapeutic alliance, and a higher education.[135, 139-141] There are both baseline[135] and time-series[142] data approaches to modelling these outcomes. One could further suspect that adherence to ICBT by MI-ANXDEP is related to their cardio-specific anxiousness and depressiveness, and also cardiac disease severity in addition to established predictors for adherence. CVD patients' adherence to treatment is well researched with respect to medical compliance[63] but not regarding ICBT for patients with MI-ANXDEP.

Further possible but untested predictors for adherence to ICBT by MI-ANXDEP can be calculated from the patients' direct responses early in therapy through written text messages, a key feature of most ICBT treatments. These linguistic variables capture aspects of what patients actually write to their ICBT therapist, they are largely unexplored, and have never before been investigated in the context of ICBT for MI-ANXDEP.[143-146] One could for instance expect that more verbally inclined patients are likely to be more adherent to verbally demanding ICBT, and are likely to write longer and more complex texts. Patients' overt, written answers to a standardised homework assignment at the start of ICBT in U-CARE Heart likely also constitutes a proxy for more covert adherence factors, e.g. treatment motivation, treatment credibility, and therapeutic alliance. Linguistic predictors may therefore bring additional predictive power to more commonly used predictors when combined in a statistical model that predicts adherence to ICBT.

1.5.5 Smoking

Smoking is one of the major modifiable risk factors for death and MI, both before and after diagnosis of CHD. Compared to the general population, smoking is overrepresented among patients with acute MI. For instance, 26% of Swedish patients with MI were current smokers at the time of hospital admission in 2016,[147] whereas 11% of the total Swedish population reported as current smokers in 2016.[148] Overall, improvements in reaching the target goal for smoking lags behind other important targets for secondary prevention, such as targets for blood pressure and blood lipids.[147] The corresponding proportion current smokers was 45% among first-time MI patients < 75 years old that were either current or previous smoker at hospital intake for MI in 2015. This figure diminished sharply during the course of 6-10 weeks as only 15% reported as current smokers at first CR follow-up. Roughly one year later, however, approximately 20% report as current smokers at the second follow-up.[149]

The weak improvement in attaining the smoking target by patients with MI may seem somewhat surprising as (a) the benefits of abstaining from smoking are substantial and clearly documented in the literature,[150, 151] and (b) individual patient-doctor smoking counselling being broadly implemented across CCUs and considered a cornerstone of comprehensive CR.[35, 40, 51, 53, 152, 153] This state is also frustrating from a public health perspective since safe, and more effective treatments than patient counselling, for instance pharmacotherapy for smoking abstinence, are available but insufficiently used.[53, 154]

A problem for the clinician to tailor more potent interventions to a new patient lies in the fact that there are no risk models developed for predicting smoking. Risk models usually predict hard endpoints. In these models, smoking is often entered as a risk factor that predicts the target outcome, it is not the target outcome itself. The Swedish unselected nationwide registries however provides a unique and underused opportunity to build accurate prediction models based on large, high-quality data,[155] not only for predicting hard endpoint risk[24, 156] but also for predicting clinically relevant behavioural outcomes such as the risk of future smoking abstinence failure. If such a model was derived for use at the start of CR, and proved to be accurate when robustly validated, the model predictions would be applicable with new MI patients at both the individual and group level. Such a model would provide a novel, probabilistic basis for clinicians to act more systematically and accurately with tailored intervention on smoking than what is done in clinical routine today. Concrete examples of possible clinical intervention based on such a model could be an extended CR follow-up schedule or perhaps even smoking abstinence pharmacotherapy prescribed at the start of CR for those patients that the model predicts as high risk for smoking abstinence failure during CR.

1.6 Aims

Within the confines of predictive and explanatory modelling, the present thesis had the following specific aims

- Investigate if psychosocial stress explains systematic variation in daily incidence rates of MI in the population.
- Test the ATC theoretical model predictions of these MI rates.
- Investigate if young adulthood CA explains middle-age statin adherence in post MI males.
- Explore the relative predictive power of both established and novel predictors for adherence to ICBT in the U-CARE Heart trial for MI-ANXDEP patients.
- Derive and externally validate a prediction model that, from the start of CR, predicts the one-year risk of smoking abstinence failure for patients with MI that were either previous or current smokers at hospital admission.

1.7 Ethical considerations

Ethical approval was submitted and granted for Studies I-IV and they adhere to the Declaration of Helsinki.

One key aspect of conducting research in an ethical manner is data protection. The risk of violating the protective rights with respect to (a) sensitive personal information (individual patient data) or (b) patient health, when conducting observational research using only pseudonymised registry data without any form of intervention is low. This applies to Study I, II, and IV. Standard procedure included that researchers only have access to pseudonymised data while the Social Board of Health and Welfare is responsible for linkage and keeping the code key safe. Pseudonymised data is handled on encrypted Uppsala University hard-drives on password protected and theft tagged computers. Original pseudonymised files received from the Social Board of Health and Welfare are kept locked in a safe. The key to the safe is locked in another safe at the University premises. Both are in turn kept in locked rooms. To access the outside of these rooms requires individual passcode and key card for building entry. Data used for Study III was gathered in an internet-based trial for which ethical approval was also sought and granted. Gathering of new trial data was done through a breach-protected internet platform with double authentication for login, run on the University server and more. In other aspects, data in Study III was handled in the same way as data used for the other studies. Since U-CARE is also a sanctioned provider of healthcare to patients, additional security aspects and patient safekeeping is also followed.

For study II, assessing CA in patients and modelling it as predictive of statin adherence, may seem unethical to some. One can however take the exact opposite stance on the basis of ethics. Given that CA is important for predicting statin adherence, ignoring it would entail unethical scientific practice by failing our obligation to try to understand and model statin adherence for these patients to the best of our ability – to derive as solid knowledge as possible. The fact that CA is ignored in much of preventive cardiology likely leads to a risk of misunderstanding of a patient's cognitive capacity for statin adherence, and ignoring CA on purpose can thus be viewed as unethical. Patients with low CA have a higher risk of failing to maintain a range of health-promoting behaviours. Is CA even considered when a new patient presents in CR with a recent MI?

In study III, there was significant non-adherence in the preceding U-CARE Heart trial, probably in part because patients with fairly low levels of symptomatology were randomised under ecologically valid conditions. The risk of detrimental effects of ICBT exposure or ICBT drop-out/non-adherence was also considered. The aim of modelling possible reasons for non-adherence would logically be the ethical thing to do for this particular trial. Patients with risk of suicide or severe depression were also excluded, yet followed-up within a strict time-frame by the patient-assigned licensed psychologist or the stand-in licensed psychologist in charge so that adequate clinical follow-up external to the trial was available to these patients.

Study IV uses predictors that are not only clinical but also SES variables. Having income as a predictor may be viewed as unethical because of integrity-breach, however, model accuracy likely takes precedence, especially if treatment is to be guided by the developed STOPSMOKE model in the future. STOPSMOKE can also handle missing data to some extent, in the case that a patient does not want do disclose some personal information. STOPSMOKE also suggests important ethical improvements over current clinical practice since a more systematic and objective assessment of a patient's risk of CR smoking abstinence failure is provided by STOPSMOKE.

See the individual papers for their respective ethical review board decisions and further information about study-specific ethical aspects.

2 Methods

2.1 Data sources

Table 1. *Sources of data for Study I-IV*

	Study I	Study II	Study III	Study IV
RIKS-HIA	X	X	X	X
SEPHIA		X		X
SMHI	X			
SEPA	X			
STA	X			
MCR		X		
PDR		X		
U-CARE			X	
SS				X
CDR		X		X

X marks usage. Swedish source name in parenthesis below. All sources are of nationwide registry type with the exception of U-CARE. CDR, Causes of Death Registry (Dödsorsaksregistret); MCR, Mandatory Conscript Registry (Mönstringsregistret) – INSARK (Inskrivningsarkivregistret) the digitalised and selected cohort of MCR; PDR, Prescribed Drug Registry (Läkemedelsregistret); RIKS-HIA, Registry of Information and Knowledge about Swedish Heart Intensive care Admissions; SEPA, Swedish Environmental Protection Agency (Naturvårdsverket); SEPHIA, SEcondary Prevention after Heart Intensive care Admission; SMHI, Swedish Meteorological and Hydrological Institute (Sveriges Meteorologiska och Hydrologiska Institut); SS, Statistics Sweden (Statistiska Centralbyrån); STA, Swedish Transport Agency (Transportstyrelsen); U-CARE, Uppsala university psychosocial CARE programme.

2.2 Study I

Wallert, J., Held, C., Madison, G., & Olsson, E.M.G. (2017). Temporal changes in myocardial infarction incidence rates are associated with periods of perceived psychosocial stress. A SWEDEHEART national registry study. *American Heart Journal* 191:12–20.

2.2.1 Hypotheses

As defined by the ATC model, time periods of particularly high and low ATC were hypothesised to induce high and low psychosocial stress and in turn respectively align with time periods of particularly high and low MI rates in the Swedish population. More compactly, ATC → stress → MI triggering that oscillate in intensity in partial unison across time.

Particularly high stress and MI rates were thus predicted during days belonging to (i) Mondays which mark the start of the workweek, (ii) the turn of the month due to possible administrative deadline stress or financial stress, and (iii) the often stressful turn of the year coinciding with the celebration and family gatherings during the winter holidays. In contrast, low stress and MI rates are predicted during (iv) weekends and (v) the 4-6 weeks of paid summer vacation in the middle of the Swedish summer. Since Swedish summer vacationing peaks in July[97], a yearly trough in population MI rates was predicted during July relative to the remaining months of the year. Since the weekend is arguably the period of the week with the least stress, it was predicted that weekends should have the lowest daily MI rates of the week. Additionally, we hypothesised that the Monday increase in MI rates would be more pronounced in the working compared to the retired population.

2.2.2 Design

This observational study of the Swedish population used SWEDEHEART RIKS-HIA data on 156,690 cases of MI registered during eight years from 1st January 2006 through 31st of December 2013. The main analysis included all cases. Secondary analyses involved eight subgroups (Male, Female, Working, Retired, First MI, Recurrent MI, STEMI, NSTEMI). Main exposure was defined as particular days belonging to certain periods of the year, and main outcome was defined as adjusted daily MI rates of hospital admission date for MI in the Swedish population. An alternative outcome was defined as adjusted daily MI rates but using the symptom start date. Control variables were locally weighted daily temperature (present day of MI and delayed 1-3 days), locally weighted daily NO_2, locally weighted age, monthly total net travelling in and out of Sweden by air. Local weighting was proportional to where in the country the MIs of a particular day occurred, e.g. average temperature calculated across the weather stations geographically closest to the MIs of that

day. This provided control for both known confounders of MI incidence rates (temperature, air pollution), and also previously suggested but yet untested confounders (delay of seeking appropriate care, abroad travelling). See *Figure 7* for details of the different data sources.

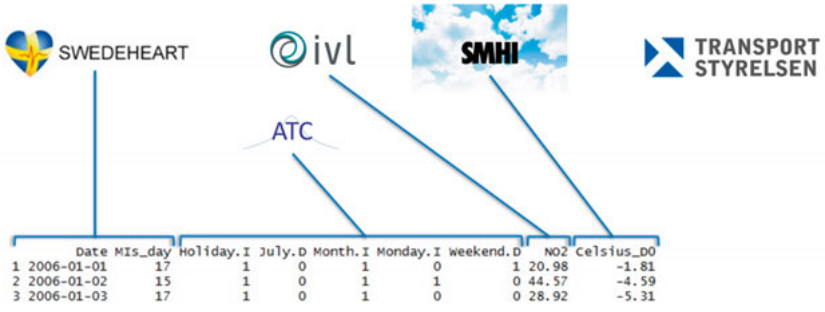


Figure 7. **Different data sources and how these were modelled for Study I.** ATC: Artificial Time-Constraint (Wallert, Oral presentation, European Society of Cardiology Congress, ESC, Rome, Italy, 26-31 August, 2016).

2.2.3 Modelling

Since the outcome variable was count data with enough counts per day (Md = 53, IQR = 47 – 60), we assume a Poisson distribution of daily MI counts (y) conditional on a set of independent variables $(x_1, \dots, x_k)$. We can then write $(y \mid x_1, \dots, x_k \sim \text{Poisson})$. Poisson regression (Eq. 1) can then estimate the partial coefficients for different dummy-coded time periods through

$$log(E(y|x_1, \dots, x_k)) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 +, \dots, + \beta_k x_k + conf + w \quad (1)$$

where (log) represents the log-link, (β_0) the intercept and $(\beta_1, \dots, \beta_k)$ are the estimated coefficients for MI counts (y) during days belonging to the different time periods $(x = 1)$ relative to MI counts during the remaining control periods $(x = 0)$. Here, $(conf)$ signifies the temperature and other potential confounders, and the additional parameter (w) representing overdispersion, which in the present study was weak.

Since Poisson regression is a multiplicative model, being a special case of the generalised linear model, and because we analysed rates of daily MI counts within time segments of equal length (24 hours), the exponents of the estimated coefficients constitute Incidence Rate Ratios (IRR). IRRs can be interpreted as factor changes. In other words, an IRR of 1.15 equals a 15% increase in daily MI rates during the defined exposure period, compared to daily MI rates during the control period. 95% profile likelihood confidence bounds (CIs) were calculated for the point estimates. Statistical significance was set to 5% (two-tailed). Covariates were checked for log-linearity against

the outcome and through plotting the standardised deviance residuals against the log predicted values which confirmed model appropriateness. Bonferroni-Holm correction was applied to the main analysis P-values to counter Type 1 error inflation by multiple comparisons. Modelling was performed in R (Version 3.2.0, R Development Core Team, Austria, Vienna) with packages *MASS*, *sandwich*, *vcd*, and *zoo*.[32]

2.2.4 Operationalization of the exposure

A day was defined as 00:00 AM – 11:59 PM. MI rates on days belonging to periods of interest with which to compare MI rates during the control period (remaining days) were chosen as follows.

Predicted increases (-I) in MI rates for days belonging to the

1. winter holidays (Holidays-I) = 15 December – 6 January,
2. turn of the months (Month-I) = 4 days before and after the turn,
3. Mondays (Monday-I) = Mondays.

Predicted decreases (-D) in MI rates for days belonging to the

4. summer vacation (Summer-D) = 1 July – 31 July,
5. weekends (Weekend-D) = Saturdays and Sundays.

2.3 Study II

Wallert, J., Lissaker, C., Madison, G., Held, C., & Olsson, E.M.G. (2017). Young adulthood cognitive ability predicts statin adherence in middle-aged men after first myocardial infarction. A Swedish National Registry Study. *European Journal of Preventive Cardiology* 24(6):639-646.

2.3.1 Hypotheses

Higher young adulthood CA estimated on average 30 years before the MI is associated with a higher risk of one-year statin adherence, and two-year statin adherence post MI. The robustness of these associations was investigated via adjusted modelling.

2.3.2 Design

This observational study used the same SWEDEHEART RIKS-HIA registry data as in Study I but instead merged with the secondary preventive registry SEPHIA, INSARK, and PDR. Limiting the sample to patients registered up

until 1st December 2011, a final sample of 2613 first-time MI males of age 60 years or younger with complete data on all variables of interest was selected. The exposure CA was constructed from the four Standard nine (Stanine) psychometric tests that these patients took during their mandatory conscription when they were 18-20 years old. Outcomes were statin adherence during the one year, and two year observation period post MI. An additional 1448 patients had incomplete data and for secondary analyses these were imputed and modelling was repeated for this completed dataset of 4061 patients.

2.3.3 Exposure operationalisation

Construction of CA was preceded by Principal Component Analysis (PCA) performed on the four tests score variables. PCA can extract latent variables, i.e. principal components (PC) from higher dimensional data, in this case test scores. As the interest was in the most essential estimate of human intelligence, the aim was to distil Spearman's psychometric *g*, or more pragmatically, verify whether a simple unit weighted average of test scores fulfilled all necessary criteria for *g*. It turned out it did, since all four test scores loaded similarly and substantially onto the first PC (loadings ranging between -0.54 to -0.47), and because this first PC explained 64.6% of the total variance in test scores and was the only factor with an eigenvalue >1 (1.61), in line with previous similar research.[59, 104] Inter-correlations of the four psychometric tests and their composite *g* were very similar to those in *Figure 8* taken from a similar sampling. As always when correlating psychometric tests scores in a large enough sample, the positive manifold manifests itself.

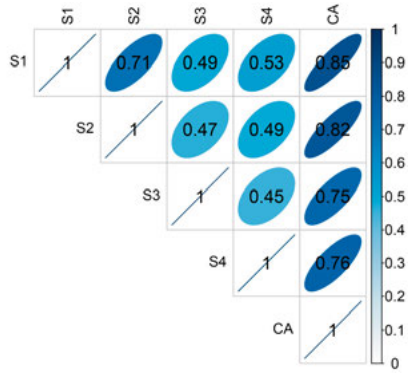


Figure 8. **The positive manifold.** Correlation matrix (Spearman´s rho) of the four psychometric subtests from the Swedish Enlistment Battery and their unit weighted aggregate estimate of *g* for first-time MI male patients aged 60 years or younger as registered in SWEDEHEART RIKS-HIA 1st January 2006 through 31st December 2011. *N* = 5,680. S1-4, psychometric subtests that estimates verbal ability, logical reasoning, visuospatial ability, and technical understanding; CA, young adulthood cognitive ability. (Wallert, Poster presentation, American Heart Association, AHA, Scientific Sessions, New Orleans, USA, 11-16 November, 2016).

2.3.4 Outcome operationalisation

All statin prescriptions for the two years following the acute MI were selected, assuming a standard dose of one pill per day. One statin pill per day is the typical dosage, corresponding with ~98% of all prescriptions in Sweden.[124] Patients on automatic medication administration were removed to avoid artificial adherence. Each patient's medication possession ratio (MPR) percentage (Eq. 2) for the one-year and two-year adherence periods was calculated as:

$$\text{MPR} = \frac{N\ pills\ obtained\ in\ observation\ period}{N\ days\ in\ observation\ period} * 100 \quad (2)$$

Two observational periods were defined, one and two years after the SEPHIA1 follow-up. As the SEPHIA1 follow-up occurred 6-10 weeks after the MI, there was a time period prior to the observational periods when individuals could pick up medication. Swedish reimbursement regulation allow for up to a three month supply to be picked up at a single pharmacy visit. Patients could therefore possibly have leftover pills entering the study. To account for this, we calculated the number of pills dispensed between the MI and SEPHIA1, and subtracted from it the number of days in that time period. Any leftover pills were added to the total for the observation period. A person had to have an MPR of ≥ 80% to be classified as adherent, in line with the common cut-off in the literature.[123]

2.3.5 Covariates

As there are likely multiple reasons patients adhere to their statin medication, inclusion of covariates was liberal. Some covariates have documented influence on adherence but were not likely to impact young adulthood CA (for instance previous stroke), and these were adjusted for to increase statistical power. Other covariates were known from beforehand to be partial proxies of CA (e.g. smoking[119]) and were controlled for in secondary analyses while also assuming an attenuation of the CA – statin adherence association (i.e. overadjustment). Acute cardiac care covariates at the time of MI were age, smoking, diabetes, hypertension, body mass index (BMI), previous stroke, employment status (working, pensioner, other), systolic blood pressure (SBP), heart rate (HR), and binary discharge medications (β blockers, angiontensin-2 (A2) receptor blockers, angiotensin-converting enzyme inhibitors (ACE) inhibitors, and diabetes medication. From the SEPHIA1 CR registration for first follow-up 6-10 weeks post MI, covariates were self-assessed exercise, participation in the CR physical activity programme, self-reported level of

mobility, self-care, usual activity, pain/discomfort, and symptoms of anxiety/depression (EQ-5D).[157]

2.3.6 Modelling

Bivariate comparisons were qualitative comparisons of means and proportions across groups and are restricted to the sample under study. For hypothesis testing, binomial and multinomial logistic regression was applied to model crude and adjusted associations with CA dependent on whether the particular outcome was binary (Adherence) or ternary (Smoking). Equidistance between the three factor levels of smoking was not assumed and ordinal logit was consequently not used when modelling CA on smoking.

Assume a binary dependent outcome $(y), pr(y = 1)$. The conditional probability of $y = 1$, given some independent variables $(x_1, \dots, x_k)$ can be modelled using a logistic model (Eq. 3). This model linearly relates $(x_1, \dots, x_k)$ to the log odds of the event that $y = 1$:

$$\log\left[\frac{pr(y = 1|x_1, \dots, x_k)}{(1 - pr(y = 1|x_1, \dots, x_k)}\right] = \beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k \quad (3)$$

where (β_0) is the intercept and $(\beta_1, \dots, \beta_k)$ are the estimated coefficients. Exponentiating the coefficients then allows for them to be interpreted as Odds Ratios (OR) for the outcome. Notice the similarity with Poisson regression. Logistic regression is also a multiplicative model being another special case of the generalised linear model and both logistic regression and Poisson regression uses maximum likelihood to estimate parameters. Hence, the estimated effect size of logistic regression (OR) can also be interpreted as a percent change but now in the odds of an outcome rather than in counts per time unit, and with the difference in distribution of the outcome variable (Bernoulli, not Poisson).

Hence, these ORs represent the average percent change in the odds of having the outcome for the particular independent variable of interest when other variables in the model are held constant. If OR for CA = 1.20, then this means a 20% increase in the odds of having the modelled outcome per one unit increase in CA). CA was rescaled to have its OR represent a unit increase of 1 SD. Based on domain knowledge and causal reasoning, we also added covariates to the crude models in an additive approach to examine the robustness of the CA – adherence associations. Profile likelihood 95% CIs were calculated and statistical significance set to 5% (two-tailed).

Modelling was performed in R (Version 3.2.3, R Development Core Team, Austria, Vienna) with packages *AER, MASS, nnet, plyr, psych*, *stats,* and *rms.*

2.4 Study III

Wallert, J., Gustafson, E., Held, C., Madison, G., Norlund, F., von Essen, L., & Olsson, E.M.G. Predicting adherence to internet-delivered psychotherapy for symptoms of depression and anxiety after myocardial infarction. Machine learning insights from the U-CARE Heart trial. (2018). *Journal of Medical Internet Research* 20(10):e10754.

2.4.1 Hypotheses

With data generated in the U-CARE Heart RCT, the prediction of adherence to ICBT by MI-ANXDEP patients would be influenced by symptom severity, age, sex, educational attainment, and linguistic behaviour.

2.4.2 General design and linguistic variables

Recruiting from 25 Swedish hospital, this trial randomised 239 MI-ANXDEP patients to either the treatment group (117 patients) or control group (122 patients). Treatment was self-tailored and psychologist-supported 14-weeks of ICBT. Control group was TAU. After excluding those that did not perform any homework assignments, 90 patients with data at the start of treatment were available for modelling adherence. An important benefit was that treatment included a collection homework assignments of which the first two assignments were the same (standardised) for all patients. This kept the clinician side of the written assignment constant across patients when the prediction of adherence was made, at the Time-point of Prediction (ToP). This allowing the first written patient behaviour to vary – free of clinician-patient dynamic effects – and to be included as predictors for adherence. The initial standardised homework assignment consisted of a brief written introduction and an 8-item questionnaire with free-form answers where the patient was asked to describe the MI and their psychological reaction to it, their present mental state, social support, and the patient's own goal(s) with partaking in ICBT.[16]

Treatment was thereafter self-tailored for which the following modules were psycho-educative, highlighting standard CBT principles such as negative feedback from depressive symptomatic behaviour, guided exposure to apprehensive stimuli, relaxation training, behavioural change towards long-term patient-centric goals, and relapse prevention.[16]

2.4.3 Predictors

Psychological (Wallert, Norlund, Olsson), cardiologic (Held), and linguistic (Gustafson) expertise guided the initial domain-knowledge predictor selection, producing 34 possible predictors to be used for further modelling, similar to other studies.[24, 158]

In particular, a patient's written answer to the initial standardised homework assignment provided data from which the following quantitative *linguistic* variables were extracted: number of words used, mean sentence length, rate of word classes (adjectives or adverbs, possessive pronouns, personal pronouns), mentioning of the MI, and the extent of patient usage of particular keywords pre-specified by the authors from the standardised homework questions presented to the patient. The reasoning behind selecting these seven predictors was their adherence-relevant proxy status for verbal ability, and patient treatment investment/belief in ICBT. See the Appendix of Study III for further details on the linguistic predictors.

Additional predictors were *demographic/socieconomic* (age, sex, marital status, education, country of birth), *clinical* (HR, SBP, BMI, alcohol consumption, current smoking, adherence to CVD medication, psychotropic medication, other ongoing counselling/psychotherapy), *psychometric* (CAQ: Cardiac Anxiety Questionnaire fear, avoidance, attention, total, [159] ESSI: ENRICHD social support instrument total, [160] EQ5D: VAS, symptoms of anxiety/depression,[157] MADRS: Montgomery-Åsberg Depression Rating Scale total, [161, 162] BADS: Behavioral Activation for Depression Scale-short form total, [163] HADS: Hospital Anxiety and Depression Scale anxiety, depression, total,[164] and *other* (n days from MI to treatment allocation, preferred way of contact).

2.4.4 Modelling

The outcome was adherence to ICBT which was binary coded as completing ≥ 3 homework assignments representing ≥ 21% of total treatment. Non-adherence was defined as < 3 completed assignments. This chosen cut-off is clinically relevant as it differentiates patients that continued with the self-tailored portion of ICBT treatment from those that only performed the initial standardised part of treatment. This cut-off also rendered fairly balanced classes which is especially important for being able to build a binary classifier with a moderate sample size.[165]

Twenty-nine of 34 predictors had complete data. The other five predictors were fairly complete (range of missing percentage 11.1 – 6.7% of total samples). The mechanism for their missingness was assumed to be conditional on observed data. In other words missing data points were assumed missing at random; MAR, but not missing completely at random; MCAR.[166, 167] Missing data points were thus imputed using *k* Nearest Neighbour (*k*-NN)

matching and the median of $k = 3$ closest values on the Gower distance metric.[168] The *k*-NN algorithm and chosen distance metric is often used for imputation when variables are both numeric and categorical, and much of the correlational structure in data is preserved when *k* is set low.[48, 169, 170] Another benefit of imputing with *k*-NN compared to multiple imputation is that one completed dataset is produced from *k*-NN, rendering subsequent analyses faster and more straightforward. Imputing missing data before deriving the prediction model for ICBT adherence means that, if the model would be implemented in future clinical practice, the corresponding imputation model would also have to be implemented as some future patients will likely present with incomplete data at ToP. The purpose of the present modelling was however not to produce an implementable risk model but instead to generate hypotheses by comparing the relative strength of both established and novel predictors for predicting the target.

Additional statistical decisions involved reporting numeric/categorical summary statistics as mean (SD)/count (%), reporting bivariate P-tests, and prediction point-estimate accuracy for the binary outcome target with 95% CIs with P-value statistical inference (tested model versus a hypothetical null model).

2.4.4.1 Random forest

For solving the present multifactorial prediction problem, a model was needed that could gauge the relative importance of different predictors while accounting for both main and higher order effects. The choice fell on a random forest (RF) model, specifically Breiman and Cutler's version of RF which combines bootstrap sampling of data for constructing each decision tree, and random subselection of predictors at each decision node.[171, 172] RF is a well-established non-linear model that is often appropriate when data size is moderate, is robust against multicollinearity, and has been applied previously to similar MI patient data[24] The optimisation metric was accuracy and ranking of predictors was based on Gini importance across CART trees[172] in the RF ensemble.[165] Gini importance, i.e. the reduction in node impurity across trees, depends on how early in the decision tree's development a predictor is selected. Thus, a predictor chosen as root split for many trees gets a higher Gini importance than a predictor chosen less frequently and/or for descendant node splits.[165]

The RF model was considered appropriate for modelling adherence with multiple highly correlated psychometric predictors in < 100 MI-ANXDEP patients. The small sample size obviously made the modelling more susceptible to sampling error, and there was not enough data for external model validation with unseen data. If then applying a flexible model such as RF, potential overfitting is a problem. RF was therefore run within a wrapper resampling of 3x10-fold cross-validation,[173, 174] when executing the final modelling step of backwards stepwise algorithmic feature selection through

Recursive Feature Elimination (RFE). Resampling with k-fold cross-validation randomly splits data into k sections (folds), fits the model k times while each time excluding the kth fold and then testing the trained model on that hold-out fold, and finally averages estimates across hold-out folds. Repeated cross-validation simply extends this process by new random fold allocation of observations per each pass of regular cross-validation.[175]

2.4.4.2 Software

Linguistic variables were pre-processed with AntConc version 3.4.4m (Waseda University, Tokyo, Japan, 2017) [176] and annotated with Stagger (Stockholm University, Sweden, 2017) [177]. Modelling and plotting was performed with packages *caret, data.table, foreign, ggplot2, ggpubr, ggthemes, mice, scales, tableone,* and *VIM* in the programming environment R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria, 2017) [32]

2.5 Study IV

Wallert, J., Pingel, R., Schön, T.B., Olsson, E.M.G., Madison, G., Hallqvist, J., Geale, K., & Held, C. Derivation and validation of STOPSMOKE. An instrument built from Swedish population data for predicting smoking abstinence post myocardial infarction. (2019). *Submitted*.

2.5.1 Hypotheses

This multivariable prognostic risk modelling study hypothesised that the derived STOPSMOKE model would be accurate and externally valid for predicting one-year smoking abstinence failure in patients with first-time MI, with predictions made at the start of CR (ToP).

2.5.2 Design

Data used to develop STOPSMOKE were taken from the SWEDEHEART acute registry (RIKS-HIA), secondary preventive registry (SEPHIA), and Statistics Sweden (SS).

2.5.2.1 Patient inclusion/exclusion

Patient selection resulted in a final study population of 28,413 patients. Their selection involved several decisions, as depicted in *Figure 9*. To attain unselected population coverage, patients with reinfarction and patients older than the upper-age coverage of mandatory SEPHIA data registration (<75 years) had to be excluded because the follow-up in such patients is subject to

sampling bias and high demands were put on the generalisability of STOPSMOKE predictions. Moreover, patients that did not even attend the first secondary preventive CR follow-up (SEPHIA1) were excluded since STOPSMOKE is intended for patients that at least initiate CR after first-time MI and because registration of patient data is conditioned on attending SEPHIA1. One could further motivate this exclusion by the logical fact that only those attending CR are likely to have any possible benefit of CR. This is critical as STOPSMOKE predictions are intended as an implemented probability basis for one-year smoking abstinence in the CR context. Based on STOPSMOKE predictions, future CR smoking interventions can then be tailored specific patient/risk group. For a similar reason, patients that initiated CR but died before the second CR follow-up (SEPHIA2) were excluded as it for natural reasons is impossible to predict their smoking status. However, only 1.6% in the present study population die before SEPHIA2 and interventions on smoking guided by STOPSMOKE predictions would likely have been similarly beneficial in the counterfactual situation that these patients had not died. Furthermore, patients who were *either* current smokers *or* previous smokers at hospital admission for MI were included. The reason for this is that STOPSMOKE has to be applicable to all first-time MI patients with a reasonable risk for failing on the smoking abstinence goal at the second follow-up. This meant not only including current smokers but also remittent smokers that reported as previous smokers at SEPHIA1 but then came back and reported as current smokers at SEPHIA2. For the target outcome, 9180 patients had missing data and were excluded.

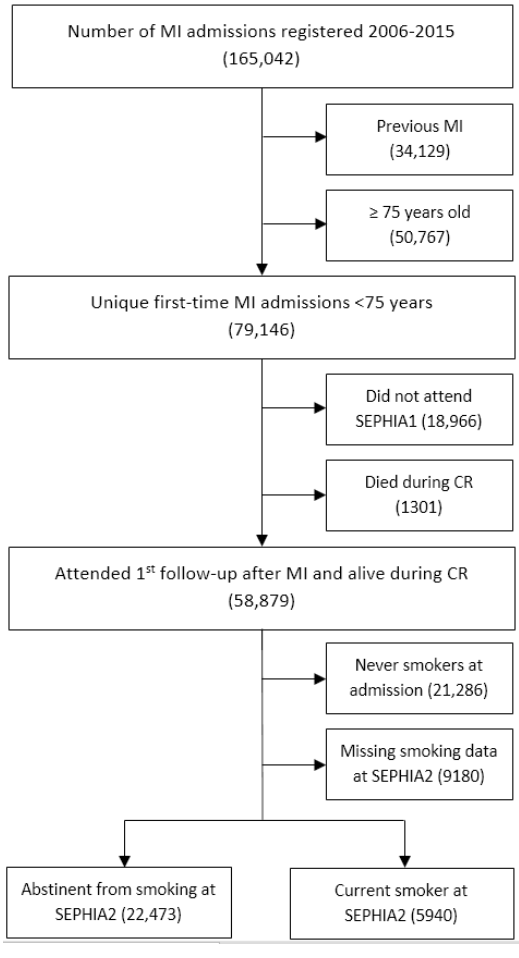


Figure 9. **Patient flowchart.** Counts are in parenthesis. CR, cardiac rehabilitation; MI, myocardial infarction; RIKS-HIA, registry of information and knowledge about Swedish heart intensive care admissions; SEPHIA, secondary prevention after heart intensive care admissions; SEPHIA1, 1st CR follow-up 6-10 weeks post MI; SEPHIA2, 2nd CR follow-up 12-14 months post MI.

2.5.2.2 Outcome and possible predictors

The outcome target was either smoking abstinence (target success) or currently smoking (target failure) at the SEPHIA2 follow-up 12-14 months post MI.

Multiple possible predictors were available up until the ToP (SEPHIA1). See page 6 in Study IV manuscript and *Figure A3* in its appendix for individual specification of these possible predictors. These are sorted into different predictor types (clinical, socioeconomic, demographic, and other). Clinical predictors are further categorised according to their temporal order (clinical history, acute before hospital admission, actual admission, hospital stay, discharge, and SEPHIA1 follow-up). Variables available after SEPHIA1

were possibly predictive of the target yet had to be discarded as these violated the ToP.

2.5.2.3 Predictor pre-processing

Predictor pre-processing involved pre-specified steps:

a. Human (author) domain knowledge: 1008 predictors reduced to 181.
b. Dummy (algorithmic) coding of categorical predictors: 181 increased to 246.
c. Human (author) screening of predictor overlap and data quality: 246 reduced to 213.
d. Removal (algorithmic) of near-zero variance predictors: 213 reduced to 158.
e. RFE (algorithmic) 3x7 cross-validated resampled selection of the final strongest predictors: 158 down to 31 (with train/test data from years 2006-2014 after excluding year 2015 validation data).

Figure 10 is the corresponding visual schematic for steps (a) – (e), the following internal validation of the final model (train-test), and final external validation.

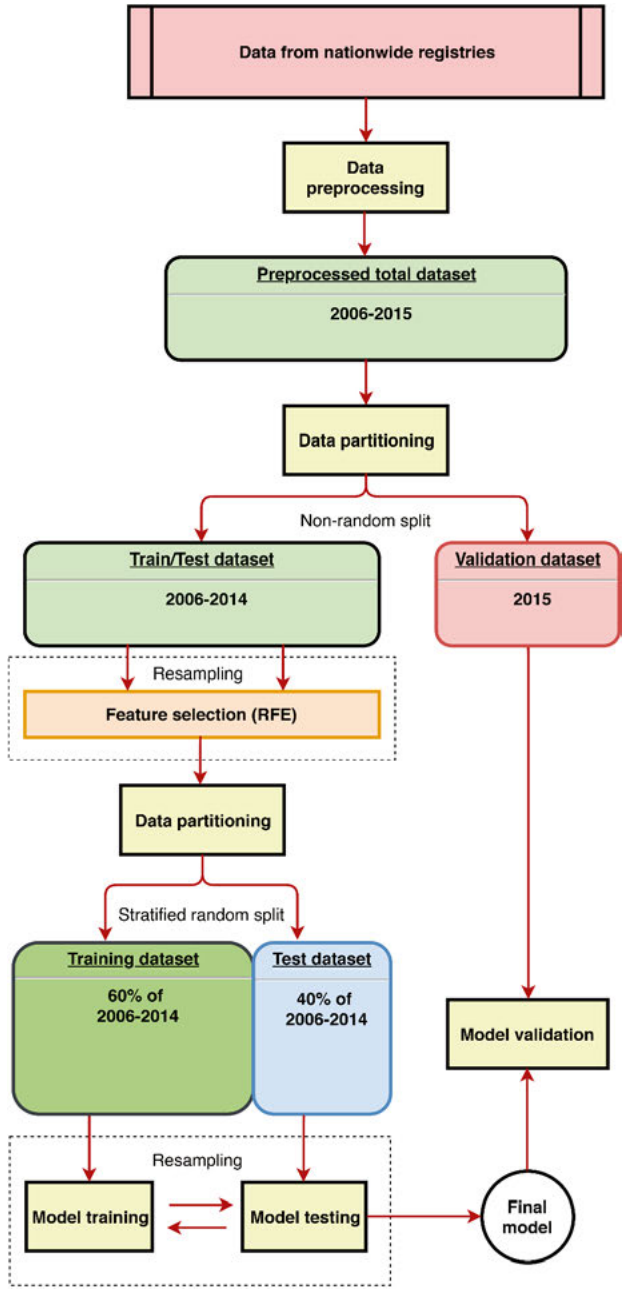


Figure 10. **Modelling flowchart.** Procedural steps of STOPSMOKE model derivation and validation. RFE, recursive feature elimination. (Wallert, Moderated poster presentation, EuroPrevent, Lisbon, Portugal, 11-13 April, 2019).

2.5.2.4 Model derivation, testing, and validation

After pre-processing, hold out of external validation data from 2015, and RFE feature selection, 2006-2014 years of data was randomly partitioned with stratification on the outcome rendering 60% of data (smoking abstinent 12,113; current smokers 3212) for model training and 40% (smoking abstinent 8074; current smoker 2141) for model testing. Naturally occurring proportions of the target were thus kept after partitioning. Predictors were centred to 0 and scaled to unit variance.

Within 3x7 cross-validation resampling, STOPSMOKE was trained as a linear support vector machine (SVM) using stochastic down-sampling of the majority class, tuning with 30 instances of incremental grid search for the Cost function, while optimising on AUROC. The choice of a linear SVM for the present large-scale, binary classification problem was motivated by an SVM being less sensitive to outliers than, say logistic regression, and that a linear kernel (i.e. no kernel at all) would be sufficient as our previous modelling with SWEDEHEART data has not produced clinically significantly better results using flexible non-linear models – including deep neural networks – compared to linear logit (e.g. [24]). Grid search tuning of the slack variable (cost function) is quite crude, and there are more advanced ways to find the optimal hyperparameter settings,[158, 178] yet for the present purpose it was deemed sufficient. Tuning the cost function is equivalent to varying the degree of spatial overlap allowed between classes when SVM fits the separating two hyperplanes to find the maximum margin hyperplane in their middle. Since an SVM outputs raw scores that are not directly interpretable, Platt scaling of the raw output was applied to produce an output interpretable as probabilities.

The trained STOPSMOKE model was thereafter subjected to the unseen test set and performance was averaged across 3x7 cross-validation resampling to ensure that there was no internal overfitting between training and testing of STOPSMOKE.

After model testing, STOPSMOKE was finally subjected to the unseen validation set of data from the most recent year (2015). This critical evaluation allowed for non-random temporal bias to influence model performance and arguably constitutes a form of external validation according to the TRIPOD (EQUATOR) guidelines on clinical risk model development.[179] The validation set was thereafter split into pre-defined male, female, <65 years, and 65-74 years subcohorts, to evaluate if STOPSMOKE was accurate also in these clinically relevant subgroups. In addition to the correctly classified proportion of cases, STOPSMOKE was also evaluated with respect to calibration of observed versus predicted smoking abstinence proportions to assess whether also the predicted probabilities output by STOPSMOKE could be used as percentages of risk.

2.5.2.5 Support Vector Machine (SVM)

An SVM[180, 181] operates by creating a multidimensional space where each dimension in this space is mapped to one of the predictors. Each individual case is represented by a point in this space, labelled as belonging to some class (e.g. either smoke abstinent or not). SVMs are then constructed by automatically fitting a separator function through multidimensional space so that the separation margin between the two classes is maximised, using the support from individual points closest to each other but with opposite labels (the support vectors). To achieve better model fit to data, the kernel used as a divide between the classes can be selected among a number of linear or non-linear functions. If extended with a non-linear kernel, an SVM can separate linearly inseparable classes. Having only a linear kernel means having a more parsimonious model, i.e. having no kernel at all as no transformation of predictor space is done. Moreover, so-called hyperparameters of the SVM can be tuned to further improve model fit (e.g. the radius if using a spherical kernel for the SVM). An SVM is a non-probabilistic classifier so to derive probabilistic classification the raw SVM output has to be rescaled to produce interpretable predictive probabilities, similar to how a logistic layer is often the final layer applied to the raw, uninterpretable output in a deep neural network.

2.5.2.6 Software

Data cleaning, modelling, and plotting was performed with packages *AppliedPredictiveModelling, caret, ggplot2, Hmisc, foreign, kernlab, lattice, mlbench, MLmetrics, plyr,* and *pROC* run in R[32] version 3.4.3.

3 Results

3.1 Study I

Due to registry duplicates and one case missing hospital admission date, 163 rows were excluded, rendering a final sample of 156,690 cases of MI. Summary statistics are available in *Table 2*.

Table 2. Patient event characteristics during different periods and all days

	Holiday-I (9,835)	Month-I (41,246)	Monday-I (25,338)	Summer-D (11,935)	Weekend-D (40,255)	All days (156,690)
Age (yrs)	72.5 ± 12.3	71.8 ± 12.3	71.2 ± 12.4	71.7 ± 12.4	71.7 ± 12.6	71.8 ± 12.4
Male sex	63.9	64.0	65.1	63.2	63.4	63.7
Heart rate	83.4 ± 23.3	81.9 ± 23.3	81.8 ± 23.2	81.5 ± 23.6	82.7 ± 23.8	82.0 ± 23.4
SBP	146.6 ± 29.9	145.9 ± 29.8	147.1 ± 29.6	144.8 ± 29.4	145.8 ± 30.1	146.0 ± 29.9
Smoking	18.6	19.5	19.6	20.0	20.1	19.5
Diabetes	23.7	23.0	22.2	22.3	22.6	22.7
Hypertens.	50.2	48.8	47.8	48.9	49.1	49.0
History of						
MI	33.1	31.5	29.8	30.7	32.2	31.2
Stroke	10.3	10.0	9.4	9.9	10.3	10.1
PCI	16.6	16.2	16.0	15.7	16.1	16.0
Job status						
Pensioners	73.2	71.6	70.5	71.0	71.1	71.5
Working	18.0	19.1	20.2	19.2	19.9	19.2
Other*	8.8	9.3	9.3	9.8	9.0	9.3
Infarct type†						
STEMI	23.7	21.7	21.2	21.8	23.6	22.1
NSTEMI	50.7	47.7	48.9	47.7	46.3	47.8
Unspec.	25.6	30.6	29.9	30.5	30.1	30.1

Values are mean ± 1 SD or % of total. Counts are in parenthesis. * includes unemployment, sick-leave, and unknown job status. † STEMI/NSTEMI was only registered from 1st January 2008 through 31st December 2013. MI, Myocardial Infarction; NSTEMI, Non-ST-segment elevation MI; PCI, Percutaneous Coronary Intervention; SBP, Systolic blood pressure; STEMI, ST-segment elevation MI. (Wallert et al, 2017, *Am Heart J*[47])

3.1.1 Main analysis

Controlling for present day and delayed temperature, population MI admission rates varied systematically with high rates coinciding with periods

perceived as particularly stressful, and low rates corresponding to periods perceived as particularly calm. Compared to control days, adjusted daily MI incidence rates were higher on Mondays (+11%) and the winter holidays (+7%) and lower in the weekends (-12%) and during the vacation month of July (-8%), but not for the turn of the Months (+1%). See *Figure 11*.

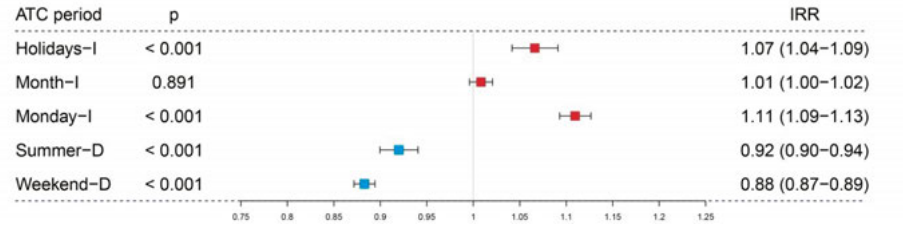


Figure 11. **Adjusted main analysis result.** Point estimates with 95% CIs indicate the factor change in daily MI rates from daily MI rates during control days (vertical grey line). Colours indicate hypothesised coefficient direction, compared to control days. The p-values are Holm-Bonferroni corrected. CI, Confidence interval; IRR, Incidence Rate Ratio; ATC, Artificial Time-Constraint. (Wallert et al, 2016, Abstract supplement, *Eur Heart J*[182]).

3.1.2 Ancillary analyses

Adding air pollution (NO_2) data available for a subpopulation registered in the largest cities in Sweden (N cases of MI = 39,634) only altered the Holidays-I coefficient, which was rendered borderline significant (IRR = 1.04 [1.00 – 1.09], $P = 0.049$), and since NO_2 was not significantly associated with the outcome (IRR = 1.00 [0.99 – 1.00] per $\mu g/m^3$ increase, $P = 0.38$), and because we already had extensive control for temperature (a proxy for air pollution) in the model, NO_2 was excluded from further analyses.

Adding total net population travelling by air to the regression model minimally weakened the Summer-D estimate (IRR without travelling = 0.920 [0.900 – 0.941]; IRR with travelling = 0.925 [0.903 – 0.946]) and left the rest of the model unchanged with travelling not being associated with the outcome (P = .82).

To investigate whether there was delay in seeking appropriate care explaining the main findings, symptom start date was modelled as alternative outcome (available for 95.6% of all MIs, N = 148,176) with recalculated local weights for control variables. This rendered slight attenuation towards the null of the Monday-I (IRR = 1.09 [1.07 – 1.11], P < 0.001) and Weekend-D (IRR = 0.96 [0.95 – 0.97], $P < 0.001$) estimates. However, they still remained substantial in terms of effect size and statistical significance, and the rest of the model coefficients did not change.

The main findings were also largely robust in the eight subgroups. Specific variations to this overall pattern were that the Monday-I was greater for males (N = 99,827) than females (N = 56,825), those still working (N = 30,131) had the greatest Monday-I compared to pensioners (N = 111,931) and to the other

six subgroups, that the Holiday increase was exclusively driven by pensioners compared to those working, STEMI (N = 34,138) had a weaker Weekend-D than NSTEMI (N = 73,858). Furthermore, first MI (N = 106,724) had a weaker Weekend-D, a greater Monday-I, and a weaker Holidays-I, compared to recurrent MI (N = 48,960) as indicated by z-tests of bivariate subgroup estimates (all $P < .05$). Stratified analyses details are available in *Figure 12*.

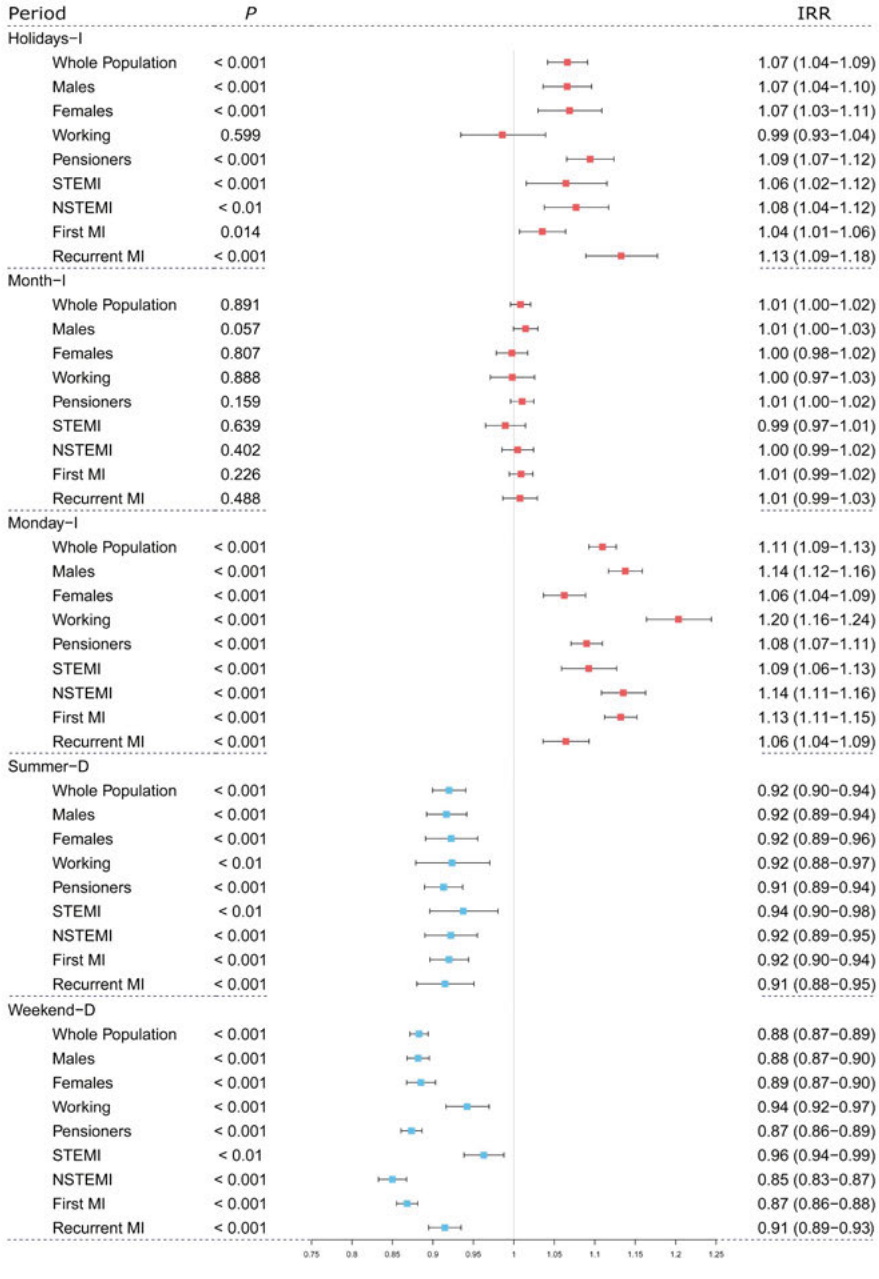


Figure 12. **Adjusted result during different periods relative to control days for the whole population and subpopulations.** Squares (point estimates) with error bars (95% CIs) represent the partial factor change in daily MI rates by defined exposure period compared to control days (vertical grey line). Whole population P-values are Holm-Bonferroni corrected. IRR, Incidence Rate Ratio; MI, Myocardial Infarction. (Wallert et al, 2017, *Am Heart J*[47])

3.2 Study II

Summary characteristics (M[SD] or count (%)) across 2,613 complete cases showed that one-year adherence to statin medication was 89.7%, and two-year adherence was 85.2% according to PDR dispensation data. Data on one-year self-reported adherence was available for 2,153 patients, and 2,047 (95.1%) of those patients reported that they were taking their statin medication.

Data in RIKS-HIA revealed that PDR-defined statin adherent patients had a higher CA for both the one- and two-year observation period (4.88[1.50]; 4.89[1.50]), compared to non-adherent patients (4.67[1.47]; 4.69[1.52]).

Adherent patients versus non-adherent patients also had a somewhat higher HR (76.6 vs 74.3), higher BMI (28.1 vs 27.1), were less likely to smoke (39% vs 50.6%), less likely to have diabetes (4.7% vs 6.0%), more frequently employed (89.7% vs 86.2%), and had a higher prescription of non-statin discharge medications (ACE inhibitors 71.1% vs 61.7%; A2 blockers 5.6% vs 3.3%; Anticoagulants 3.0% vs 2.2%; β-blockers 93.3% vs 87.7%).

Summary characteristics for adherent vs non-adherent patients at the time of SEPHIA1 revealed more frequent daily physical activity (one-year follow-up 4.3[2.8] vs 4.2[2.5]; two-year follow-up 4.3[2.8] vs 4.0[2.6]), less self-reported pain/discomfort (some pain/discomfort 33.2% vs 37.5%), and higher participation in CR programmes (Attending Heart School 41.6% vs 33.1%; Physical exercise training 36.1% vs 26.4%; Stress management course 6.8% vs 5.2%; Nutritional course 12.5% vs 11.5%). Groups were similar regarding their age, SBP, hypertension, self-reported mobility, self-care, usual activities, and emotional distress.

Due to the design of the study, the whole sample was considerably younger than the total population registered in RIKS-HIA (See *Table 1* in Study I).

3.2.1 Main analysis

Crude logit models in *Table 2* estimated an average one-year 15% and a two-year 14% point estimate increase in the odds of being statin adherent per one SD increase in young adulthood CA.

3.2.2 Ancillary analyses

Multivariable modelling available in *Table 3* show that the aforementioned main analysis estimates were (a) minimally attenuated when adjusting for background CV risk factors, (b) minimally strengthened with additional adjustment for discharge medications, whilst (c) substantially attenuated when further adjusting for health related behaviour, with (c) rendering an average one year 11% and two year 8% odds increase for being statin adherent per one SD increase in CA.

Table 3. *Crude and adjusted effect sizes per one SD increase in CA for one-year and two-year statin adherence after first-time MI*

		Exploratory adjusted results		
	Crude main result	Age, Age^2, Weight, Comorbidities, and Employment	Age, Age^2, Weight, Comorbidities, Employment, and Medication	Age, Age^2, Weight, Comorbidities, Employment, Medication, Smoking, Programme participation, EQ-5D
One-year adherence	1.15* (1.01, 1.31)	1.15* (1.01, 1.31)	1.16* (1.02, 1.32)	1.11 (0.97, 1.28)
Two-year adherence	1.14* (1.02, 1.27)	1.12* (1.00, 1.25)	1.13* (1.01, 1.26)	1.08 (0.96, 1.21)

Values are point estimate ORs with 95% CIs for complete cases (n = 2,613). CA, young adulthood cognitive ability; EQ-5D, European Quality of Life Five Dimensions Questionnaire. MI, myocardial infarction, SD, standard deviation. OR, Odds ratio.*$P < 0.05$. (Wallert et al, 2017, *Eur J Prev Cardiol*[60])

Since adding health promoting behaviours attenuated the main association of interest between CA and statin adherence, separate additional adjustment for single components of health promoting behaviours was performed. This revealed that only smoking was responsible for the attenuation of the adherence ~ CA association. Multinomial logit was therefore performed to model CA on smoking. Substantial associations (OR [95%CI]) were found insofar that a one SD increase in young adulthood CA corresponded to a average reduction in the odds for being a current smoker (0.60 [0.55, 0.66]) and former smoker (0.79 [0.71, 0.88]), with never smoker as reference category.

Assuming that missingness in data was not completely at random (MCAR) but instead to some degree dependent on available data (MAR), we sought to account for possible introduction of bias in the complete case main analysis. The same regression analyses was therefore repeated after multivariable imputation via chained equations and predictive mean matching,[183] using a similar procedure as reported in[16, 48, 50, 62] yet the results were basically the same as in the complete cases analyses. Results after imputation are available in the Appendix for [60].

3.3 Study III

Among MI-ANXDEP patients randomly allocated to ICBT and also adherent to ICBT were less likely to be male, rated themselves as higher in cardio-specific anxiety, especially so for the fear and attention sub-dimensions, used more words in their written answers to the homework assignment, and wrote more of the pre-defined mutual words. Adherent patients also showed a tendency for being older and to rate themselves as having more depressive symptoms. The two groups did not differ statistically with respect to their highest attained education, country of birth, civil status, clinical variables, number of days from MI to treatment allocation, or in their stated preferred route of in-treatment contact.

3.3.1 Main analysis

After initial predictor selection by experts and k-NN imputation, the resampled RFE procedure was run and it settled on 19 out of 34 predictors (56%). This final model outperformed the null model (point estimate accuracy [95% CI], *P* for trained model vs null model), although showing room for accuracy improvement (0.64 [0.61, 0.68], < 0.0001).

Exploring the relative predictive power of the 19 predictors, their resampled relative importance as decided by the RF algorithm was rescaled, sorted by predictor class and importance, and plotted in *Figure 13* showing that the six strongest predictors for adherence to ICBT among MI-ANXDEP patients were the CAQ fear subscale score, sex, the number of words used, CAQ total scale score, the average sentence length, and the number of mutual words used.

There were no ancillary analyses in Study III.

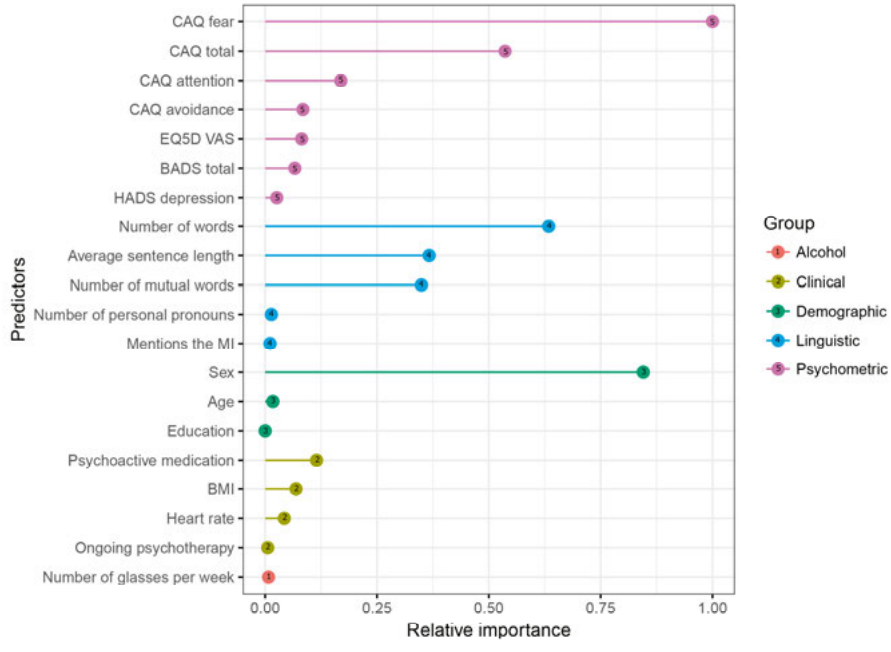


Figure 13. **Relative importance of each predictor in the final model for adherence.** Predictors are sorted by importance and type and rescaled with the strongest predictor (average highest cross-validated reduction in decision node impurity) scoring 1.00 and the remaining predictors in relative fractions. The discarded predictor education is included for reference. (Wallert, Poster presentation, European Society of Cardiology Congress, ESC, Munich, Germany, 25-29 August, 2018).

3.4 Study IV

3.4.1 Derivation cohort summary statistics

The derivation cohort included both the training (n = 15,325), and testing (n = 10,215) datasets from years 2006-2014. However, stratified random partitioning of the derivation cohort into these two large dataset was predetermined to produce highly similar summary statistics across sets. Thus, only the training set summary statistics are reported from the derivation cohort.

Regarding *SES*, patients with primary (lowest) education were 33.2%, and those belonging to the 1st (lowest) decile of family adjusted income were 8.3% in the training dataset. *Hospital admission* smoking was reported by almost half (48.1%) of patients, snuff (smokeless lip-pouch tobacco) was used by 7.9% of patients, mean age was 61.4 (8.3) years, weight 83.4 (15.5) kg, height 173.9 (8.5) cm, LDL-C 2.1 (0.6) mmol/L, HDL-C 1.2 (0.4) mmol/L, SBP 149.4 (27.9) mmHg, DBP 87.5 (16.5) mmHg, and 44.0% were currently working. *At the ToP SEPHIA1 follow-up*, 15.1% were current smokers, 10.1%

current snuff users, and 3.0% had attended a smoking cessation programme. In addition, 30.9%, 32.9%, and 3.3% had participated in physical training at the hospital, heart school, and a stress management programme, respectively. Patients also reported an average 4.3 (2.7) sessions of physical activity of moderate intensity for at least 30 minutes per session. The patient proportion of readmission for any cause post hospital discharge up until the first follow-up was 13.1%. The CR Q4 target average sum was 2.2 (0.8) and the corresponding binary target (4 out of 4 pivotal CR targets achieved) was attained by 7.4% of patients. *At the outcome target SEPHIA2*, 21.0% of patients were current smokers.

3.4.2 Summary statistics comparison across cohorts

Below are the bivariate comparisons of the validation cohort with the above summarised training cohort.

With respect to *SES variables*, the validation cohort had a smaller proportion with only primary education (28.7%), whereas roughly the same proportion in the lowest income category (8.6%), and somewhat fewer were currently working at the time of the MI (42.5%). *Hospital admission* data revealed slightly lower proportions of current smokers (45.2%), but higher proportions of current snuff users (13.8%), a slightly higher mean age (62.2 (8.3), and weight 84.5 (16.1), but lower LDL-C 1.9 (0.7), and similar values across cohorts for height (174.0 (8.8), HDL-C 1.2 (0.4), SBP 151.3 (27.8), and DBP 88.5 (16.3). At the *SEPHIA1 ToP,* the validation cohort was similar regarding the current smoking proportion (15.0%), and slightly more likely to be current snuff users (12.1%). No one attended a smoking cessation programme (0.0%) in the validation cohort, a decline in comparison. Somewhat fewer patients in the validation cohort attended Heart School (31.5%) and stress management (2.6%). Conversely, more patients attended physical training (36.3%) yet their leisure physical activity was instead a bit lower with an average of 4.1 (2.6) weekly sessions. Patients in the validation cohort were also less likely to be readmitted to hospital between discharge and SEPHIA1 (11.2%), and more likely to fulfil the Q4 target, both as the sum of targets 2.5 (0.9) and binary (15.5%). At the *SEPHIA2 outcome,* however, a similar 20.4% in the validation cohort were current smokers.

3.4.3 RFE predictor ranking

Figure 14 displays the cut-off for the final predictor set as decided by RFE and their individual relative importance for predicting the smoking target at SEPHIA2.

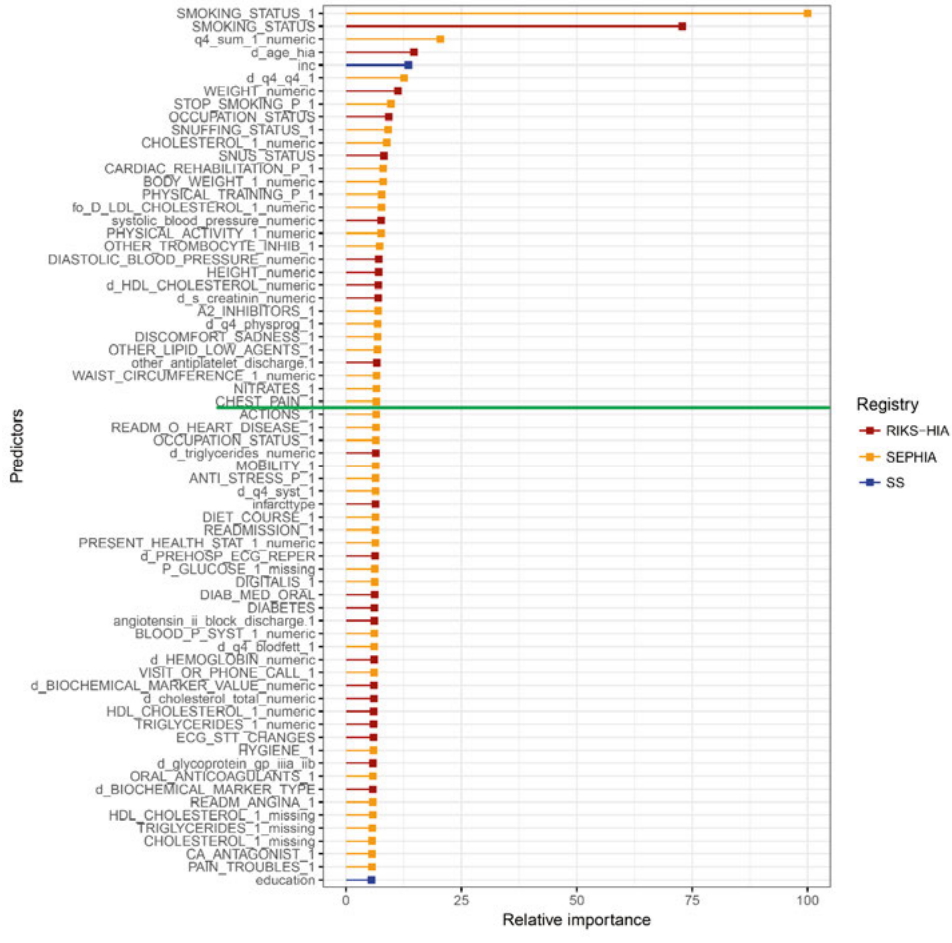


Figure 14. **Relative importance of predictors.** Horizontal predictor lines (needles) length represents the relative importance of predictors for the binary target of smoking abstinence 12-14 months post MI in <75 year old patients enrolled in CR that had been either current or previous smokers at hospital admission for first-time MI. Predictors are ranked by their average reduction in node impurity. The green horizontal line represents the cut-off chosen by the RFE algorithm with resampling, excluding predictors below this line. RFE was run on all data excluding the most recent year (2015) of validation data. N = 25,540. SEPHIA Secondary preventive SWEDEHEART registry, first CR follow-up; SS, Statistics Sweden; RFE, Recursive Feature Elimination; RIKS-HIA, Acute care SWEDEHEART registry.

3.4.4 Internal validation

Internal validation (n = 10,215) of the trained STOPSMOKE model showed excellent performance (Accuracy [95%CIs], P vs benchmark null model) for predicting the target in the hold-out test set (0.826 [0.819, 0.834], <0.001).

3.4.5 External validation

The main analysis (n = 2,873) revealed similarly excellent STOPSMOKE performance at predicting the unseen hold-out validation set (0.846 [0.832, 0.859], <0.001). See *Table 4* for the corresponding confusion matrix and additional model parameters.

Further external validation in pre-defined patient subpopulations of males (n = 2,102), females (n = 781), younger <65 years (n = 1,529), and older 65-74 years (n = 1,344) also showed excellent performance of STOPSMOKE yet with some variability in terms of accuracy among males (0.845 [0.829, 0.860], <0.001), females (0.860 [0.831, 0.882], <0.001), < 65 year old (0.796 [0.776, 0.817], <0.001), and 65-74 year old (0.907 [0.890, 0.922], <0.001) subpopulations.

Table 4. *Main analysis confusion matrix of patient counts and additional STOPSMOKE performance metrics when it predicts the full validation cohort*

		Observed	
		Failure	Success
Predicted	Failure	487	342
	Success	100	1944

Sensitivity	0.830
Specificity	0.850
Positive Predictive Value	0.588
Negative Predictive Value	0.951
Null Model Prevalence	0.204

Patients that were predicted by STOPSMOKE to either fail or succeed with the smoking abstinence target at SEPHIA2 (Predicted) are tabulated against the actual failures and successes (Observed). n = 2,873.

Exemplifying the result with a new hypothetical patient younger than 75 years, having had her first-time MI 6-10 weeks prior, reporting as either previous or current smoker at hospital admission, and just starting CR:

1. Using no model, the patient has an average base rate 20.4% one-year risk of being a smoking abstinence failure at the end of CR.

2. If STOPSMOKE is used and it predicts failure, the patient then has an average 58.8% risk of smoking abstinence failure at the end of CR.

3. If STOPSMOKE instead predicts success, the patient then has an average 4.9% risk of smoking abstinence failure at the end of CR.

Hence, by using the STOPSMOKE algorithm for the differentiation of patients (58.8% vs 4.9%) corresponds to a risk ratio of 12 for the target.

3.4.6 Other analyses

Model calibration was done in the validation set through binning of patients in deciles of their predicted probability for smoking abstinence failure at SEPHIA2, which were then plotted against the observed proportion of smoking abstinence failures within each bin. Calibration was fair at best, showing that STOPSMOKE overestimated probabilities for the target in the low-midrange (20-50%) of observed risk. Note that calibrated probabilities are not necessarily of importance for assessing the accuracy of a binary classifier. A model with suboptimal calibration only means that the individual predicted probabilities cannot be treated as directly proportional to the observed risk probabilities.

4 Discussion

4.1 Are all models predictive models?

The present thesis suggests that they are. In study I and II, the research questions are causal, whereas for Study III and IV they are purely predictive, yet regardless if a prediction of a causal effect is made or a pure prediction – at their core remains the estimate, the projection, the forecast, of what is suggested to be true in a hypothetical future. The problem is that all predictions of the future are uncertain to some degree, and by that, all models are also false to some degree. By no means does this this suggest that all models are equally wrong, at least not from a pragmatic standpoint. Instead it stresses the continuous need for careful judgement to assess the level of uncertainty of a prediction, and the level of usefulness of a model. Note that the realisation that all models are predictive models does not contradict the different A – C classes of models suggested in the introduction to the present thesis (*Figure 1*). There is no contradiction because that model classification deals with answering specific research questions dependent on study designs, whereas the fact that all models are ultimately simplified predictions of reality comes from the inescapable global limitation of modelling in itself.

4.2 Briefly on modelling and scientific knowledge

As described in the Introduction, observational designs for causal research questions are in general subject to bias by the lack of control for potential residual confounding because there has not been random exposure allocation. A spurious association of the exposure and an outcome may therefore be misinterpreted as being causal while the causal relationship is instead with one or several unmeasured variable(s). This limitation applies to both Study I and II. It is however not always possible to randomise to an exposure of interest. The reasons for that may be ethical or practical. A sufficiently powered RCT may take years to complete and is often costly per patient. In fact, the current reproducibility crisis – by no means restricted to the discipline of psychology alone, although psychology was first to systematically address the problem – is to a considerable extent rooted in overinterpretation of results from underpowered experiments.[184, 185]

Randomisation to "stress" to ascertain its possible causal effect on triggering of MI would neither be ethical, nor cost-effective. Causality can still however be inferred with a decent probability. Smoking is yet another example of an exposure for which a trial is unethical – but we still conclude its causal effect on, say, cancer and mortality. Granted, the effect sizes for smoking on such outcomes are very large, yet where do we draw the line for when non-RCT findings may be assumed to be causal? Another common weakness with RCTs is in their sampling of only a select portion of the population, and a lingering uncertainty to what extent the causal effect estimated in the sample actually generalises to the population.

Luckily, minimising such sampling bias is often the core strength when conducting observational research with nationwide health quality registry data on practically unselected patient populations. Powered by such data we take good aim at causal inquiry when we, for instance, systematically rule-out alternative explanations by controlling for measured confounders as done in Study I and II. There are also more advanced ways to estimate causal effects with observational data, including designs with an instrumental variable,[186] regression discontinuity,[187] or Mendelian randomisation.[188]

If we succeed in estimating a causal effect is however a different matter. It is a matter of human judgement. The answer to that is rarely binary but rather placed on a continuum of certainty. To exemplify, an underappreciated aspect in observational research is that controlling for measured variables also results in proxy control for unmeasured variables to a degree. This complicating example speaks directly against the oversimplified approach of leaving matters of causality exclusively to randomised trial designs.

For pure predictive models, the issue is fairly straightforward. Causality can be ignored since it is not directly relevant to the aim of producing accurate predictions that generalises to new observations.[1] Prediction models alone are however not enough. But robust and accurate predictions are useful estimates of risk that can inform both clinicians and patients, as well as policy makers. Predictive models can also be used in research for deciding how to target intervention trials aimed to have causal effect. New deep learning models that can use many predictors more freely and effectively also represents a largely unexplored possibilities for diagnostics, prognostics, and hypothesis generation. Often, these models level with, or even surpass, human benchmark performance[20, 21, 189] and come with the additional benefit of machine-type consistency, cost-effectiveness, and objectivity across patients.

To this writer it is clear that non-RCT designs have their place in research, and can to some extent with their strengths offset weaknesses inherent in RCT designs.[190] This author suggests that we can, and should try – to the extent possible – estimate causal effects in the real-world from observational data when, for instance, limited data, funding, or ethics prohibit large RCT designs. We should probably also do such observational research when prohibiting factors for conducting an RCT are not present. Historically, it is obvious that

both randomised and observational study designs have brought about useful, valuable knowledge. And this author views them as complementary at getting as close as possible to the root of causality, prediction, and truth.

For that purpose, this author finds the falsification approach by Popper to be useful,[98] if coupled with a logically coherent verisimilitude (truthlikeness) criterion as further developed by Hilpinen.[99] This criterion can be used to rank our theories on their closeness to truth, based on both their level of theoretical specificity and degree of factual support. With this philosophical theory we can constantly refine our applied scientific understanding of the causal and predictive web of the world, knowing that our suggested models will remain tentative[6] to the extent that they will be simplified[8] – and to that extent also erroneous – because they have to fit the human condition. Ultimately, humans – scientist or non-scientist alike – perceive, think of, and act on cognitive representations of the world, not the world itself.

4.3 Specific discussion of Study I-IV results

The main objectives were to apply different methodologies to forecast MI and behavioural outcomes related to CR. Below follows a brief discussion of the strengths and limitations of our findings and a few educated guesses about a foreseeable future.

4.3.1 Psychosocial "stress" and triggering of MI

Study I focused on the rather abstract and complex phenomenon of stress, a latent variable, and the triggering of MI. It was the first study to model this in the Swedish population of MI rates across time. As predicted by the ATC theoretical model outlined in this thesis, incidence rates of MI were lower over weekends and during the July vacation month, yet higher on Mondays and through the winter Holidays, compared to remaining control days. The only theory-dissonant finding was a lack of effect over the turn of the Months. Sensitivity analyses showed that the main findings were predominantly robust after controlling for temperature, air pollution, cross-border travelling by air, in eight clinical subpopulations, and after modelling symptom start as alternative outcome to hospital admission. The unique Swedish registry data allowed for thorough control for both known and suggested-but-previously-untested confounders. The ATC model of stress and stress-triggered somatic events held up well to these attempts at falsification. The present findings also corroborate the aggregate of previous research findings[88-94, 191, 192] showing that MI rates oscillate with substantial degree of structure through time. The conclusion to be drawn from Study I is that it is probable that psychosocial stress has a causal effect on the well-known systematic changes in MI incidence rates across time in the population.

The methodological application of Poisson regression to count data in Study I is common, and has previously been applied to SWEDEHEART MI rate data.[43] However, to the extent of our knowledge, previous research has not defined periods of both particularly low *and* high stress based on specific stress theory (ATC) and hypothesised corresponding MI rates in the population. Despite that this seems reasonable, given that culture and previous empirical findings taken together indicates that psychosocial stress oscillates over time around some average level of stress in society. Defining both "ups and downs" and the automatic definition of more average stress period for days that are left undefined suits Poisson regression in a straightforward way.

Another interesting aspect of modelling in Study I was the use of symptom start date as alternative outcome. The result suggests that delay of seeking appropriate care only partly explain the fluctuating MI rates. Out of the five hypothesised periods, it is perfectly reasonable that the Monday-I and Weekend-D were the two periods which estimates changed when we modelled symptom start date as alternative to hospital admission date. These are the two periods that lie directly adjacent to each other in time and have the shortest durations, and consequently, are most susceptible to confounding by delays in seeking appropriate care.

Regarding patient health, it seems important that both the public health perspective and the clinical perspective does not lose track of psychosocial stress with respect to MI triggering. Recommending individuals at high risk to avoid unnecessary stress seems reasonably precautious. Important improvements for further studies include a more precise measurement of stress in the population over time, and the need to expand the present study design to other countries were sociocultural periods of high and low stress are different with respect to the Julian calendar. The novel theoretical framework allows for clearly defined a priori hypotheses to be tested in a more scientific manner than post hoc reasoning after empirical modelling has been done. Although there are no obvious clinical uses of the model today, it might become useful in a more centralised and digitised future cardiology.

4.3.2 CA and statin adherence post MI

In Study II, young adulthood CA was robustly associated with both one-year and two-year statin adherence approximately thirty years later in a large sample of first-time MI male patients prescribed statins for the first time. CA was also predictive of smoking. We know from previous findings that CA is the global cognitive capacity influencing more specific subordinate cognitive functions, such as understanding, memory, and executive function. The present findings thus suggest that lower levels of CA in these patients has a negative effect on them taking their recommended statin medication post MI.

Study II expands the field of cognitive epidemiology to the CR setting post MI. Linking different Swedish high-quality population registries, including

SWEDEHEART, was crucial for this study. The present result complements the bulk of earlier research showing that individuals with low early-in-life CA are less likely to successfully manage a range of lifestyle risk factors.[59, 112, 113, 118, 125, 193-196]

The lack of acknowledgement of CA in international consensus CVD guidelines suggests that CA deserves more attention. Interestingly, guidelines mention several variables (e.g. education, health literacy, physical activity, smoking, dietary habits, medication adherence) known to be either predicated on, or virtual proxies of, CA, yet underlying CA is ignored as if it did not exist.[35, 37, 51, 113, 197, 198] Maybe the reluctance to acknowledge CA in healthcare is because it is such a hard-to-grasp latent phenomenon? Or is it because it is not readily intervened on with treatment?

One can look at this from a different angle, where research on CA can contribute to a better understanding of patients' differing abilities to take care of themselves. Acknowledging that patients differ in their CA would allow for future cardiac care to tailor itself with respect to CA. Tailoring interventions with respect to CA has been done routinely for a long time in other fields, such as education and geriatric care which are both required to take the individual's ability into account. Many of these tailoring practices may be exportable to cardiology. In addition, the stability of CA throughout adult life actually opens a door for early primary prevention based on early-in-life CA. As long-term prediction is possible, effective early-in-life premorbid prevention might also be possible.

Much remains to be investigated within cognitive epidemiology, and the SWEDEHEART registry linkage with several other registries provides a strong foundation to further advance cognitive epidemiology for post MI patients, especially with respect to the role of CA for risk behaviours and hard endpoints during and after completed CR. Even trial designs testing interventions that are tailored to CA may be worthwhile. This is uncharted terrain, and may prove ineffective, yet then at least we know that this route to improve CR for these patients has been put to the test.

One central challenge would be to deepen our understanding of the complex interplay between CA and SES (e.g. education) on health behaviours and outcomes.[111] One part of this is acknowledging that CA, as well as educational attainment, is to a substantial extent inherited and has a polygenetic basis, and at the same time understanding that behaviour can be modified to a substantial extent by the environment.[52, 55, 199] Seeing that there is support for both of the nature and the nurture positions with respect to CR – and that they can co-exist and cross-pollinate. Post MI healthcare would likely be helped by such research, which could inform how to most effectively conduct, say, patient education post MI, because it will likely need to be different across individuals due to both modifiable and fixed factors.

Some psychometric limitations were identified in Study II, for example with the military's choice of scale representing CA. The Stanine scale is

peculiar regarding both its limited granularity (9 scaled values) and truncated distributional tails because an individual score estimate outside the ± 2 standard deviations range are automatically assigned either 1 or 9. Although few CA values were extreme in this regard, the general property of the Gaussian marginal distribution of CA does indeed allow for such extreme observations whereas the Stanine scale does not. This truncation effect was somewhat countered through the aggregation of scores across four different subtests, which likely biased the true effect of CA on statin adherence towards the null. Furthermore, the military psychometric test battery is not optimal with respect to its correlation with *g* (*g*-loadings), and because only four tests are included. This probably also underestimated the true CA – adherence effect size. Future research could therefore examine the present question using tests with higher *g*-loadings that are preferably scaled on a non-truncated, more granular, and therefore more useful CA scale (e.g. the Standard scale or T-scale).

4.3.3 Adherence to ICBT in patients with MI-ANXDEP

Study III found that adherence to ICBT for MI-ANXDEP patients in the U-CARE Heart RCT was predicted by sex and cardio-specific fear and anxiety. Adherence was also predicted by new linguistic predictors extracted from actual words written by the patient as response to the initial standardised homework treatment assignment. The result suggests that the linguistic predictors hold additional predictive power for adherence to ICBT in these patients and that linguistic predictors may act as proxies for therapeutic alliance, treatment credibility, and verbal ability.

For the development, trialling, and implementation of ICBT interventions, investigating factors that predict adherence to ICBT is of importance. This is because (i) any possible treatment effect of CBT requires treatment adherence, (ii) non-adherence to initiated ICBT is quite common and is unlikely to be effective at remedying debilitating psychiatric symptoms, and (iii) non-adherence to ICBT may aggravate psychiatric symptoms, for instance the risk of personal guilt or shame interpretation in the perception of the self with respect to non-adherence to ICBT treatment for psychologically unstable patients.

Regarding more established predictors, cardio-specific anxiety and fear were relatively strong predictors, corroborated previous findings of diagnosed depression associated with better adherence to CR.[200] That sex was an important predictor was also in line with a higher male drop-out from an internet-based depression intervention[140]. The latter is also supported by the general clinical observation of a higher female propensity for, and adherence to, psychological treatments.

Interestingly, that novel linguistic variables were predictive of adherence may be in line with most of the literature on therapeutic alliance and related

concepts considered to be supportive of adherence to ICBT.[135, 139, 140, 146, 200] These predictors represent a fairly new class of predictors that hold potential for improved predictions of adherence to ICBT and warrants further investigation. Much of the process of extracting linguistic predictors can also be automated, and would thus fit nicely with a cost-effective automatic prediction tool for ICBT adherence. Clinically, such a tool may be used early in treatment to either strengthen adherence to present ICBT or suggest a different treatment than ICBT (e.g. standard face-to-face) for a patient with a predicted risk of non-adherence.

There are important limitations regarding Study IIIs moderate sample size. The lack of sensitivity analyses was a product of "data shortage". Even though resampling is applied, repeated fitting of different models to the same moderately sized data will run the risk of modelling spurious associations. More predictors could have been used if more data had been available. The prediction model could then also have been tested using a more robust procedure, e.g. as the model in Study IV was validated in subsamples of the study population. The present prediction model is in need of external validation, and probably also redesign, before implementation is possible. The U-CARE Heart main study however showed no effect of treatment so implementation of the ICBT treatment – and the possible implementation of the framework which collects data on the present predictors for adherence prediction – is not planned.

There are some specific strengths with respect to sampling in the present study. Recruiting from 25 CCUs providing nationwide coverage, and had high ecological validity since it was performed to a large extent as part of routine clinical care. This could otherwise be a general problem in ICBT trials where recruitment might be very narrow, with only a small minority of those in need, i.e. the most motivated, answer recruitment ads in newspapers and online for ICBT treatment. Moreover, it may be that only the "clean cases" (comorbidity as exclusion criteria) make it through initial psychiatric screening and are randomised. In addition to such narrow selection, and the ensuing possible problem of "for whom is ICBT effective?", there is no possibility for blinding to treatment, and outcome evaluation may be done on subjective, self-rated psychometric scales for depression, anxiety or some other psychological disorder intended to be reduced through ICBT. From the clinical psychologist viewpoint, a request for three things from ICBT studies would be strengthened efforts towards (a) larger sample sizes at the trade-off of fewer studies being conducted, (b) a high ecological validity in the study recruitment procedure, and (c) complementary evaluation of treatment effects on more objective measurements (e.g. sleep quality, physical activity, returning to work) to the self-rated psychometric scales.

The focus on linguistic predictors led to particular exclusion of 27 patients, because responses on the initial homework assignment were required to be able to extract these predictors.

Some previously established predictors were not replicated in the present study, i.e. education, age. The reason for age being a non-predictor may be because the sample was unusually old for an ICBT trial sample. Alcohol consumption was not predictive of the target, maybe because problem-drinking was low in the sample. Nor was psychoactive medication, nor other external therapy (not an exclusion criteria in U-CARE Heart), possibly due to a homeostatic mechanism where patients seek severity-adequate treatment (e.g. external treatment is sought when symptomatology is severe). Such resources are quite available and subsidised in Sweden relative to those in countries with predominantly private health insurance. The HADS scale was a weak predictor for adherence, maybe because of psychometric shortcomings of the scale itself and/or the exclusion of severely depressed (suicidal) patients.

The present study can also be criticised for its operationalisation of adherence. There are many ways to differentiate adherence from non-adherence [201] and for the present study, we chose a fairly relaxed definition: Only requiring patients to continue treatment beyond the two initial treatment modules. This decision was in part of necessity due to the overall low adherence to ICBT in U-CARE Heart.[16] This definition also has some qualitative aspects to it, as it represents when the patient actually does anything of the self-tailored portion of the treatment, as opposed to only login and answer the standardised initial assignment. Qualitative aspects of adherence in the U-CARE trial has also been further studied.[202]

4.3.4 Predicting smoking abstinence post MI

STOPSMOKE, a novel ML instrument that predicts smoking abstinence during CR after first-time MI, was derived and robustly validated. STOPSMOKE was accurate and because it is based on real-world clinical population data from SWEDEHEART and other interlinked national registries, STOPSMOKE provides the first implementable probabilistic basis for the CR relevant risk of smoking abstinence failure.

STOPSMOKE is arguably a strong model in terms of prediction generalisability to new Swedish cases because of the nature of data used to construct and validate it. Compare data used for STOPSMOKE to the sampling for the well-established GRACE risk model, which was developed as a Cox model without Swedish patients,[66] or the Swedish SCORE risk model[203] which is also based on a fairly crude algorithm and validated for Swedish patients with only a sample in the city of Gothenburg.

International consensus guidelines are clear that secondary prevention after MI needs to be improved further,[35, 40, 51, 152] and the smoking dimension of patient risk behaviour and counselling is part of the present CR imperfection. Secondary prevention with regards to smoking holds room for improvement as only around half of current smokers at hospital admission for MI quit

smoking during CR, and more patients report to be previous smokers at the second CR follow-up compared to the first follow up, i.e. a group of patients remits to smoking during the course of CR.

Among the vast number of validated risk models available (e.g. [66]) for clinical use with MI patients, there seems to be none other than STOPSMOKE that predicts smoking post MI. The bulk of models predict hard endpoints, such as reinfarction or death, [65] which holds obvious relevance. One could however argue that so does the prediction of "softer" risk behaviours, especially as smoking abstinence is particularly in focus in the clinical context of CR.

From a clinical perspective, STOPSMOKE seems useful at both the group- and individual risk prediction level. The high risk group classified by STOPSMOKE could be targeted at the start of CR with more powerful, targeted smoking intervention than standard counselling. Two such possible interventions are (a) pharmacotherapy that facilitates smoking abstinence and (b) more frequent follow-up visits. A combination may also be most effective at increasing the proportion of smoking abstinent patients post MI. Such targeted intervention may translate into more effect CR with respect to smoking, compared to the TAU routine of today with fairly uniform smoking counselling to both low and high-risk patients.[154] For the individual patient, STOPSMOKE can be applied to generate a new empirical prediction of that patient's future risk of smoking. This risk could then be used by the clinician and patient in smoke counselling when deciding which care best suits that patient. The STOPSMOKE prediction of personal risk may also entice patient motivation to abstain from smoking.

Such a future clinical routine would require further empirical evaluation before implementation. A clinical trial design could be used to determine the effectiveness and cost-effectiveness of a STOPSMOKE-based targeted intervention, preferably the more cost-effective Registry-based RCT (R-RCT) design [75] as pioneered in Sweden, seems ideal for such a study. The R-RCT design has previously been successful using SWEDEHEART, (e.g. [76, 204]), and this design has also recently been suggested for evaluating the Heart School (patient education).[50] Another more basic trial design would be to randomise to only the availability of STOPSMOKE+TAU vs TAU. Compared to TAU, one would then hypothesise superior outcome on the smoking target, and also on hard endpoints in the STOPSMOKE+TAU group. Such a trial design would provide a sharp test of the clinical value of implementing STOPSMOKE in itself.

The STOPSMOKE model has some important limitations. For sampling reasons motivated in the Methods section, STOPSMOKE is not applicable to all patients post MI that are under risk of failing on the smoking target during CR. STOPSMOKE should therefore be evaluated in other patient subgroups, and also in other countries to the extent possible. There was also variation in the classification accuracy of STOPSMOKE, such that it seems to work best

for patients in the 65-74 year range. Some predictors were not available for training STOPSMOKE even though they are likely to be predictive of the target (e.g. alcohol consumption, psychiatric disorders). This suggest that the already accurate STOPSMOKE model could be further improved regarding its prediction accuracy. Using, for instance, psychiatric diagnoses from the Patient registry as predictors in STOPSMOKE seems worthwhile when developing future iterations of STOPSMOKE.

The inclusion of both previous and current smokers may seem like a limitation. However, given that a substantial portion of patients report as previous smokers at SEPHIA1 follow-up but then take up smoking during CR and return as current smokers at SEPHIA2 did not allow for excluding these patients, which are obviously under risk for the target. From a substance abuse perspective it is fairly straightforward to see how a patient may quit smoking abruptly in fear or shock recently after their MI, but as life then returns to normality during the course of CR, the patient risk of taking up their previous smoking habit increases.

Sometimes when evaluating risk models, their transparency and simplicity is praised. For the sake of face validity attached to a risk model, i.e. if it seems trustworthy in the eyes of clinicians and patients, such praise is understandable. However, one could argue that this is only true up to the point of all else being equal. Superior prediction accuracy of a more complex model that is less transparent must be valued higher for the sake of the patient. The present "black-box" STOPSMOKE is not transparent. There are for instance no overt coefficients to be interpreted, as would have been the case if developed as a logit model. STOPSMOKE is also fairly complex, with many predictors included. These predictors were however screened initially on the basis of clinical availability, and with digital pre-registration of these variables in the registries and implementation as part of an automated risk-prediction system, the complexity of STOPSMOKE should not burden the clinician more than would a simpler model with fewer predictors. This again underscores the point that model accuracy should take precedence over model transparency and simplicity when possible. If a patient has a predicted high risk of smoking abstinence failure, one would want that prediction to be as accurate as possible – especially if clinical intervention is to be based on that prediction.

One benefit of STOPSMOKE is that its predictions are as consistent and unbiased as only a machine can make them. Today, cardiologists and cardiac nurses tailor their smoking counselling to their patient yet such tailoring runs the risk of being influenced not only by the patient risk of smoking failure but also by the present levels of stress in the clinician, personal "chemistry" with the patient, and other human limitations. As clinical professionals, we should always strive for objective judgement and action. As human beings, we should always be aware that we will never act on, or judge anything or anyone, completely objectively.

For patients enrolled in CR after MI, the best is probably a combination of human-machine decision making, also in the instance of STOPSMOKE, where the machine outputs objective information (e.g. prediction of risk) which is then interpreted by the clinician and then decided upon together with the patient. Today's technology allows for a very promising future of having a range of prediction models based on population-representative data that deliver automatic risk estimation in a safe and ethical way for a palette of clinically relevant outcomes, all made available when a new patient begins CR post MI. As such a system would gradually be developed, it would require continuous empirical evaluation. Such a solid empirical foundation would likely be of substantial benefit to the patient, the clinician, the healthcare system, and society.

4.4 Conclusions

- Psychosocial stress seems to have an effect on the triggering of MI in the Swedish population.
- The ATC model was empirically validated and provides an alternative view of stress across time and allows for the prediction of systematic temporal variation in the population rate of stress-sensitive somatic events, such as MI.
- Young adulthood cognitive ability predicts statin adherence in middle-age males post first-time MI. This association is likely to be causal.
- Linguistic variables added to the strength of clinical predictors for predicting adherence to ICBT in the U-CARE Heart trial, generating testable hypotheses.
- STOPSMOKE was robustly developed, externally validated, and constitutes the first implementable risk model that accurately predicts the risk of one-year smoking abstinence failure at the end of CR in first-time MI patients <75 years that were either previous or current smokers at the start of CR.

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