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Chronic Disease Risk Prediction Models and their Impacts on Behavioural and Health Outcomes: A Systematic Review and Meta-analysis

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Abstract

Risk prediction models are tools that predict an individual's risk of developing a health outcome. They were developed to influence patient management by guiding preventive interventions, with the goal of reducing the incidence of new diseases. Studies examining their impacts are uncommon, and no consensus regarding their effects has been reached. This systematic review sought to determine the impact of risk prediction models for chronic diseases on physician behaviour, patient behaviour, and patient health outcomes. Twenty-two studies were found to be eligible for review. The results demonstrated that: 1) physician behaviour may be positively influenced, though a statistically significant result was not found; 2) alterations in patient behaviour were inconclusive; and 3) some aspects of patient health outcomes were significantly improved, such as changes in blood pressure, but these results may be clinically insignificant. The evidence indicates some effects may exist, though future studies are required to confirm this effect.

Keywords

Risk prediction model, chronic disease, primary care setting, systematic review, meta-analysis

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Chapter 1

1.0 Introduction

The focus of this thesis is on risk prediction models, which are clinical tools that take formal, evidence-based combinations of predictors and risk factors and generate an estimated risk for specific, often health-related, endpoints.[1] The ability to use patient characteristics for estimating the risk of an outcome, or 'event', can be applied within many healthcare settings and to many clinical outcomes.[2] This thesis will concentrate on models which are predictive of chronic health outcomes, and that are used mainly in primary care settings.

Though several definitions of *chronic diseases* exist, the term is generally applied to diseases that are of long duration, generally slow progression, and are of noncontagious origin.[3] The prevalence rate of chronic diseases, such as diabetes or heart disease, has been estimated to be as high as one in three persons in Canada.[4,5] This represents a 40 billion CAD economic burden in direct costs for disease management.[5,6] Globally, chronic diseases were responsible for 38 million (68%) deaths in 2012, with the number projected to rise to over 50 million by 2030, representing the leading cause of death worldwide.[4]

Primary care settings are the main arena within which chronic diseases are managed and their onset prevented.[7] Chronic disease prevention and management in the given climate is gaining increasing importance in primary care settings.[6] Given the increasing burden of chronic diseases, many chronic diseases and conditions are primarily managed in outpatient settings under the supervision of a primary care physician.[5,8] This creates a collaborative relationship between patient and physician, emphasizing the role of patient self-management within the context of primary care settings.[9,10] Though numerous health care professionals are involved in chronic disease management, the physician is often recognized as the locus of care.[8] Primary care was selected as the setting of interest with a particular emphasis on primary care physicians given the intrinsic relationship between chronic disease prevention and management and primary care settings.

Risk prediction models may supplement the management of chronic diseases in primary care. They function well as an educational tool by providing both physicians and patients with an objective measure of a patient's risk of disease or outcome.[11] They are intended to help *guide*, not replace, the clinical decision-making process involved in disease prevention and management.[12] To provide context regarding the development of risk prediction models, a brief explanation of their history will be provided in the following section.

1.1 The Framingham Heart Study and the birth of prediction models

The first well-accepted health-related risk prediction model was published in 1976 by researchers of the first iteration of the Framingham Study, a prospective cohort study seeking to identify the risk factors for cardiovascular disease (CVD).[13,14,15] Prior to the Framingham Study, the etiology of CVD was unknown. Indeed, the term "risk factor" wasn't popularized until 1961 with a publication from the Framingham researchers identifying the factors of risk of developing coronary heart disease (CHD).[16,17]

By the 1940s, CVD was responsible for 1 in 2 deaths amongst Americans, and was the foremost cause of mortality in the United States.[17] Former US President Franklin Delano Roosevelt's death due to cerebral hemorrhage in 1945 drew greater attention to the necessity of identifying the cause or causes of CVD.[18,19]

In recognition of the paucity of funds for research to understand and combat CVD, the National Heart Act was enacted in 1948, which authorized the funding of the Framingham Heart Study.[20,19] As a result of the study, researchers identified numerous risk factors for CVD, including age, sex, high blood pressure, smoking status, dyslipidemia, and diabetes.[21,22] The previous medical treatment paradigm began to shift towards prevention.[23] With the findings of the Framingham Study, the groundwork for preventing not just CVD but many other chronic diseases was established.

1.2 From treatment to prevention

The identification of the predictive risk factors for CVD as well as risk factors for many other chronic diseases helped promote the concept of disease prevention.[19] Through

epidemiologic investigation, the prevention of CVD became a possibility by providing a range of modifiable, targetable risk factors for intervention. The identification of risk factors allowed physicians to not only to continue to treat those afflicted, but also to target individuals at risk of disease.[19,24]

The field of risk prediction models is largely focused on CVD, which is understandable given its origins, but the principle of identifying risk factors and quantifying their independent and cumulative impact on disease risk have been applied to numerous health outcomes. For example, the Gail model was developed to predict breast cancer risk, allowing for the appropriate prescription with tamoxifen, a chemopreventive medication.[25,26] One recent systematic literature search identified 25 models predictive of the risk of type 2 diabetes mellitus.[27] More recently, the first multivariable risk prediction model for chronic obstructive pulmonary disease (COPD) was created in 2015 incorporating different genotypes in tandem with other clinical variables, such as age or smoking status, to generate a person's long-term risk of developing COPD.[28]

Risk prediction models have become a common method of identifying individuals at risk for experiencing a targeted health outcome such as cancer or diabetes; they are capable of generating an individual's absolute probability or risk of experiencing an event well before the individual experiences disease onset.[29,30] The process of estimating the absolute risk of particular diseases for individual patients is often recommended as it may help guide the preventive care activities by health care practitioners.[31]

The interactive, multifactorial nature of the causes of chronic disease indicate that preventive measures should target multiple risk factors as opposed to focusing on single factors[31,32]. For example, the risk factors of blood pressure or cholesterol levels are predictive of CVD. However, interventions focused strictly on reducing blood pressure or cholesterol levels only have a limited effect on absolute cardiovascular risk, indicating that reductions in multiple risk factors are more effective at preventing cardiovascular events.[32] Risk prediction models are often multivariable models themselves, accounting for several risk factors in one cohesive equation to generate an absolute risk of disease.[33] Reducing a patient's absolute risk of disease necessitates a multifactorial approach,

targeting multiple risk factors rather than single ones, a process that may be guided by use of a risk prediction model.

Clinical guidelines often incorporate and recommend the use of risk prediction models.[11] Indeed, one systematic review published in 2010 identified 27 guidelines that recommended cardiovascular risk assessment in asymptomatic adults, indicating a movement towards formal risk assessments for patients.[34] This shift represents a belief that model usage to estimate patient risk of disease will correspondingly affect physician behaviour, such as prescription with preventive medications, thereby affecting patient behaviours, such as lifestyle modifications, which may result in improved patient health outcomes.[33,35,36] However, though risk prediction models have become quite commonplace and increasingly recommended for use in clinical practice, consensus regarding their intended impact has yet to be achieved.[37]

1.3 Impact analysis

There have been several studies conducted regarding the development and, to a lesser extent, the validation of risk prediction models.[33] Nevertheless, their utility in clinical practice is unknown due to a dearth of information regarding their impact. Though systematic reviews have been conducted regarding the impact of risk prediction model use for single health outcomes or to assess the health economic impact of model use, no systematic review have examined impact analysis studies of risk prediction models comprehensively.[35,38] There are calls from researchers to assess the impact of risk prediction model use in clinical practice.[33,38] Given the widespread recommendations to use prediction models, there exists a lack of cohesive evidence to support their implementation for regular use in the prevention of chronic diseases.

For this reason, this thesis sought to search, collect, and collate the relevant literature pertaining to the impact of chronic disease risk prediction models on the domains of practitioner behaviour, patient behaviour, and patient health outcomes to ascertain their clinical utility in primary care settings. In doing so, a unifying perspective is provided regarding the potential impact of risk prediction models in primary care settings, thereby

establishing a foundation from which prediction models may be implemented and most effectively influence the health of the population.

1.4 Overview of thesis

This thesis was written in accordance with the requirements set forth by Western University's School of Graduate and Postdoctoral Studies. The study presented is a systematic review and meta-analysis of all studies that have conducted an impact analysis of chronic disease risk prediction models in primary care settings.

The second chapter will explore the often inconsistently used terminology pertaining to risk prediction models and present methods for their classification. Chapter 3 presents the literature relevant for the research question, outlines the rationale and need for this study, and defines the objectives used to guide the study. The methodology employed for the systematic review and meta-analysis is presented in chapter 4. The results obtained from the systematic review and meta-analysis are detailed in chapters 5 and 6, respectively. A discussion and interpretation of the results follows in chapter 7, outlining the strengths and limitations of the reported study, as well as future directions for research in this field.

Chapter 2

2.1 Introduction

The study of risk prediction models is a growing field, with an increasing number of models being developed every year for a wide array of outcomes. However, the field itself lacks a consistent method of classification for these models, with several terms (e.g. 'risk calculator', 'clinical prediction model', etc.) being used to describe similar tools. This chapter seeks to provide an understanding of risk prediction models, provide an overview of related terminology, and further classifies risk prediction models according to a few of their inherent criteria.

2.2 Understanding risk prediction models

The concept of prognosis is central to the practice of medicine, with most diagnostic and therapeutic actions aimed at improving a patient's prognosis, a term used to describe a person's future health based on a series of characteristics.[30,39] One example of a tool used to improve a patient's prognosis is a screening test, which allows for the identification persons with unrecognized disease—the early identification can afford the person and health care provider greater opportunities for treatment than if the disease had been identified later.[30,40] Similarly, risk prediction models are clinical tools that can improve a patient's prognosis. They may promote the initiation of risk reduction strategies by providing physicians and patients with an absolute risk of developing a specific health outcome, motivating those at increased risk to take preventive action.[41]

Risk prediction models generate an estimated probability that a disease is present (*diagnostic* models) or will occur in the future (*prognostic* models) by using an array of clinical and non-clinical patient characteristics.[42,30,39,37] These tools seek to determine the patient's *global risk*, a term used to describe the absolute risk of experiencing an event over a specific time period, often measured in the magnitude of years for chronic outcomes and months for acute outcomes.[43,22] Global risk is calculated using the algorithms or multivariable equations underlying the prediction models.[44] These global risk assessment tools often take into account the additive and synergistic effects between

individual risk factors, placing increases in individual risk factors, or *predictors*, into context relative to the overall disease, allowing for a continuum of disease risk to be expressed and identifying patients most likely to derive benefit from an intervention.[45]

With the uncovering of the quantitative relationship between these risk factors for disease, physicians and patients are able to more efficiently manage disease risk by targeting the global risk.[43] The estimates derived from risk prediction models may guide the management of therapeutic or ameliorative options through informing and fostering the process of shared decision making.[37,46,29] Numerous guidelines, such as those published by the National Cholesterol Education Program in the United States, the Joint National Committee, and the American Diabetes Association recommend modifying the intensity of strategies for risk reduction based on the patient's global risk.[47] Indeed, an accurate risk prediction model is of no clinical utility if it does not change behaviour and ultimately health outcomes.[48]

The estimated global risk is often stratified according to risk thresholds, such as an individual being at either low, moderate, or high risk of developing the outcome. Guidelines often recommend that treatment decisions be influenced by these thresholds; the New Zealand guidelines to manage elevated blood pressure recommend initiating treatment conversations with patients with a five-year 10% risk of CVD if their blood pressure is raised (between 150/90 and 169/99 mm Hg).[49] Though these thresholds for intervention are not necessarily based on their evidence-based impact on outcomes, but rather often representing a vestige from historically-derived levels, they do provide a simplified cut-off value from which interventions such as pharmacotherapy may be applied.[50]

2.3 How have risk prediction models been studied?

Though research in prediction models is varied, it can be categorized generally in three sequential stages: 1) model development, 2) model validation, and 3) impact studies.[37,51,52] Though the purpose of this thesis is to assess evidence from the third stage, a brief overview of the first two stages will be given.

2.3.1 Model development

The purpose of model development involves the steps necessary to create a model that can calculate the likelihood of risk with a high level of accuracy for any permutation of predictor variables in a specific population. Steyerberg (2009) outlined seven key steps to developing a model (Table 1).[30]

Table 1. Seven steps to developing a prediction model.[30,53]

Step	Purpose	Description
1	Problem definition and data inspection.	Understanding the research question, what outcome it seeks to predict, defining the predictors, with consideration of the data under study.
2	Coding of predictors.	The predictors are derived from the dataset, and it must be determined how to code the categorical or continuous variables.
3	Model specification.	Model specification pertains to predictor selection, what methods to use to select predictors, and the management of assumptions used in models.
4	Model estimation.	Once the model is specified, parameters such as the regression coefficient values must be estimated for predictors or combination of predictors.
5	Model performance.	The performance of the model, such as how closely predictions are to the actual outcome, as well as specific questions regarding the calibration and discrimination properties of the model.
6	Model validation.	To reduce the likelihood of overfitting, internal validation of the model would ensure the reproducibility of the model in the target population.
7	Model presentation.	The model can be presented as its base algorithm, or in a different format for use in practice, such as a chart, table, or computerized program.

The information necessary to construct a model is derived from a source or development population. The source of data for model development is ideally from a prospective

study of sufficient duration to allow for the natural history of disease to progress, which allows for optimal documentation of predictors and outcomes, and to obtain a more accurate measure of the baseline risk.[51] Case-control studies are less ideal as they don't allow for the absolute risk of the outcome to be calculated given that cases and controls are sampled from the source population at a ratio not representative of baseline risk. [51,54] Regardless of the study design from which the data are used to construct a model, it generally applies to a specified *target population*, a group of persons who share similar clinical characteristics to the development population.[55,56]

Predictors are identified from the data source. Predictors are factors that may be demographic in nature, include clinical history, physical examination results, disease characteristics, test results, or previous treatments.[51] Predictors are not necessarily causally related to the outcome of interest, but indicate that a patient may be at risk of the outcome, or in other words, are associated with the outcome.[51] Though a greater number of predictors that are theoretically associated with the outcome may be identified, not all can or will be included in the final model.

Model performance is measured according to two primary metrics: calibration and discrimination.[30] Calibration is a measure of agreement, or *fit*, between the expected and observed endpoints.[57] For example, if a model predicts that a person will experience the outcome with a 5% likelihood, for every 100 people with the same 5% likelihood, approximately 5 should experience the event of interest. Calibration can be assessed using the Hosmer-Lemeshow goodness-of-fit test or a calibration plot where predicted and observed outcomes are plotted on opposing axes, with perfectly calibrated models generating data points along the 45^{o} line.[57,58]

Discrimination assesses how well the model can differentiate between those who will develop the outcome of interest from those who will not.[53] With regards to prediction models, a model with high discriminatory ability can well distinguish risk groups from one another.[59] It is commonly assessed using a performance measure, specifically the concordance (*c*) statistic and the area under the Receiver Operating Characteristic (ROC) curve (AUC), which is identical to the *c* statistic for binary outcomes.[57] The prognostic

groups may be identified after the creation of a model, such as segmenting the groups according to quartiles, where the lower quartiles should have worse outcomes than the upper quartiles.[30] Defining the prognostic groups inappropriately, however, may result in a failure to discriminate between risk levels, with increases in rates of false positives or negatives.[59]

Model validation ensures that the purpose of predictive models (providing accurate predictions of risk for new patients) is met.[30] Model development generally concerns itself with internal validation more so than external validation, assessing whether the estimates derived from the model apply well to the source population.[53] Internal validation can help identify and in turn, reduce the potential for bias in model performance, such as overfitting which can lead to unfounded optimism on the part of the developer.[60] Overfitting, or when predictions derived from models are highly accurate when evaluated on the source data but have a low accuracy in alternate sets of data, can lead to an overly optimistic perception that the model will perform with the same high level of accuracy in new subjects from the underlying population.[30,61] Overfitted models tend to overestimate the risk of outcome in high risk patients, and underestimate risk in low risk patients, reducing their applicability to novel populations.[2] Identifying and reducing such biases can ensure that the model is applicable and accurate within its target population.

Validation can be conducted by using a split sample approach. In this case, the dataset is divided into the development sample and the validation sample; the model is then developed from one segment of data and validated in the next.[I] This method can be considered inefficient as not all available data are used to develop the model.[53,60] Alternate methods include cross-validation and bootstrap resampling, which are validation methods where data are resampled from the development sample.[62] In doing so, all the data are used for development, and validated within the same pool of data,

[I] In the field of Machine Learning, the "validation sample" is typically referred to as a *test set*.

ensuring the applicability of the model to the source population, as well as reducing the potential for overfitting.

With the model completed, attention is turned to the presentation of the model, or how it is presented for clinical use. Model presentation should be appropriate for its intended setting, and ease its implementation and usage. Risk prediction models generally present the *absolute risk*, or the risk of an event in a single group, as opposed to using a relative measure, such as the *relative risk*, or the ratio of risk of an event in one group to another group.[63,64] Absolute measures of risk are preferable to inform clinical decision making, whilst conversely, relative measures of risk are preferable in etiologic research.[64,65] This preference is primarily due to the occlusive nature of relative measures of risk; if one treatment option reduces risk of adverse outcomes from 5% to 2.5%, in relative terms there is a 50% reduction in risk, though in absolute terms the risk is only reduced by 2.5%.[64,66] Presenting absolute measures of risk reduces the possibility of misinterpretation compared to presenting relative measures of risk.

At their core, prediction models should allow physicians to input data and calculate or generate a measure of absolute risk.[67] Some risk prediction models present solely their predictive algorithm, requiring physicians to manually calculate the absolute risk. For example, the GUSTO-I model, which predicts the 30-day risk of mortality in patients with acute myocardial infarction, presents to the user simply its regression formula (see Appendix A for the complete formula).[68]

Similarly, researchers of the Framingham Heart Study published a cardiovascular prediction model, predicting for general CVD risk as well as individual CVD events, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, and heart failure.[22] In this model, physicians would input the patient's values for several predictors, and manually calculate the long-term risk. For example, using a Cox model, a 61 year old woman who smokes, is not diabetic, total cholesterol of 180 mg/dL, high-density lipoprotein (HDL) of 47 mg/dL, and systolic blood pressure of 124 mm Hg, would have a 10-year estimate of risk of 10.5%.[22]

Though these formulas are potentially accurate, their complexity limits applicability in clinical settings. Simplifications in delivery may increase the accessibility of the model. Researchers for the Framingham Heart Study aimed to make their complex statistical models more useful by developing and using a "points system" wherein points associated with predictors are summed, and the total score corresponds to a calculated 10-year coronary risk.[67] Technological advancements have further reduced the burden of this barrier to use of models in clinical practice, with computer systems reducing the labour and likelihood of error associated with manual imputation.[69] A transition to simpler systems can increase the routine use of prediction models in clinical practice.[69,70,71]

The generated output is not the only aspect of model presentation involved in model development. It also includes the medium of delivery. Paper-based options, including score charts or nomograms, can be an effective option for easy application in clinical settings.[53,62,71] The Sheffield Risk Table identifies the absolute risk of coronary death, and provides the risk through a table format allowing for printed copies to be easily accessible when calculating risk.[72] Reflecting technologic advancements, there has been a recent trend to program risk prediction models as either mobile phone or tablet apps, or providing web-based models that could easily calculate a person's risk of health outcome.[53] One model predicting risk of death at 14 days, and for risk of death or severe disability at 6 months after traumatic brain injury was developed; the authors chose to present the model as a web-based tool with predictors that are easily identifiable.[73] Another model predicting an infant's risk of childhood obesity is available as a mobile phone application.[74] Offering multiple formats provides options for physicians in terms of their own personal preferences, potentially easing their implementation, allowing these tools to help inform decision making and ultimately affect patient outcomes.[48,75]

2.3.2 Validation studies

The literature pertaining to prediction model research heavily favours model development studies, with a comparatively small number of studies assessing validation despite the importance of assessing model generalizability.[37] Further, though numerous guidelines detailing model development have been published, guidelines pertaining to the

appropriate methodology for validation or impact analysis are scant.[76] Most risk prediction models are found to be less accurate when used in new populations, possibly due to inadequate model development, or differences between the development and validation populations.[37,77] Despite the models potentially being internally valid, they should still be tested or validated in new individuals before implementation in guidelines or application in practice to ensure their predictive accuracy.[48]

Validation studies pertain primarily to the external validation of the model. Though internal validation, or assessing the accuracy of the model within the development dataset, is equally important to the development of the model, external validation takes the developed model with the same predictors and assigned weights and is applied to external datasets, which provide the heterogeneity necessary to mimic real life applications to determine the model's predictive performance.[37,33]

There are generally three forms of external validation: 1) temporal, 2) geographical, and 3) domain validation (Table 2).[33] Geographical and domain validation tend to be more robust forms, taking drastically different populations within which to examine the performance of the model, compared to temporal validation, which remains within the same institution from which the model was developed.

Table 2. Forms of external validation conducted in prediction model studies. Adapted from Moons et al.[33]

Type of Validation	Description
Temporal	External validation conducted on individuals from the same institution in a different time period. There generally is not any crossover of data from the development dataset and the validation dataset. It can be conducted through non-random splitting of the existing dataset based on the moment of inclusion, but reduces the amount of data used for development, with greater similarities between the development and validation populations. It can be conducted by collecting data prospectively for the purpose of validation after model development as well.
Geographical	Geographical validation examines the transportability of the model to different institutions or countries, often applying different inclusion or exclusion criteria as well as different methods of measuring predictors in those populations compared to the development population.
Domain	Domain validation is an extension of temporal or geographical validation, where the validation population differs greatly from the development population. An example of this would be assessing the predictive performance of a model for CVD that was developed in a healthy population amongst individuals with type 2 diabetes mellitus.

2.3.3 Impact analysis

Impact analysis or model impact studies determine whether or not the model: 1) is actually used by physicians; 2) guides clinical decision making; 3) modifies behaviour; 4), improves clinically relevant processes; or 5) reduces costs.[37,33] Indeed, physicians will be unlikely to use risk prediction models to inform their decision making without the evidence to support the effectiveness of models, which would be analogous to prescribing drugs on the basis of in vitro testing alone.[75] Validation and impact analysis have different goals, and therefore different study designs. Validation studies are preferably conducted on a cohort of individuals with a specific set of inclusion and exclusion criteria

applied, whereas impact studies require a comparator population.[48,78] In other words, the two groups assessed in impact studies are generally those who receive an estimated risk score (intervention) and those who do not (control).[33] At present, there are no formal guidelines for the conduct of impact analysis studies; however, there are suggestions for how to assess the impact of the use of models on clinical practice.

The provision of information is the source of the first categorization of model impact studies; is any information in addition to the estimated risk provided? Two approaches exist: directive and assistive.[33,37,78] In the assistive approach, the probability of outcome is the only generated information, while the directive approach is more suggestive, providing treatment recommendations in addition to the absolute risk.[48,79] The assistive approach is considered more respectful of physician judgment and autonomy allowing for greater interpretation of the patient's risk and subsequent treatment decisions, although the evidence suggests a greater effect is found through the directive approach.[78,80]

Comparisons between groups, namely the intervention and control groups, are scientifically strongest when the study design is a randomized trial.[48] A variant, the cluster randomized trial where the unit of randomization is the clinic or hospital, may be preferable to avoid contamination, or a learning effect where the physician alternately applies and does not apply the model in alternating patients, as well as the possibility for exchange of information between physicians at a single centre.[37,81]

Non-randomized studies, such as pre-post studies, can be conducted as an alternative to randomized studies, which can be time-consuming and costly.[33] For example, the impact of the Ottawa ankle rule, a diagnostic risk prediction model assessing for risk of fracture amongst patients experiencing ankle and foot injuries, was assessed using a pre-post study.[82,83] Where the outcome of interest does not require long-term follow-up, such as the decision making of physicians, a cross-sectional study can suffice to capture decisions immediately upon provision of the patient's absolute risk.[33]

Appropriate conduct of model impact studies can prove to be vital to the uptake of risk prediction models in clinical practice, ensuring that (validated) models help guide

treatment decisions, affect the behaviour of both physician and patient, and improve the long-term health of patients assessed for absolute risk.

2.4 Terminology

The terminology used in the study of risk prediction models is varied with many names used to describe the same basic tool.[84] Risk prediction models are often operationalized dependent on their function, presentation, or setting, which is where much of the ambiguity resides. This section presents a list of terms commonly used for risk prediction models as well as poses reasons for their distinction.

Regression models that apply to health outcomes are denoted as *prediction* models, the root term used for these tools.[77] Prediction models generate an individual's *risk*, creating the amalgam of *risk prediction model*.[84] The addition of the term 'risk' can be considered unnecessary, as models usually only provide a probability as their output, hence they are often simply referred to as prediction models in the literature. The term *clinical prediction model* can also be used, and is contingent upon the setting, specifically a clinical setting.[52] Clinical prediction models are thus tools or rules derived from systematic clinical observations, with the intention of assisting physicians in identifying patients who require diagnostic tests, treatment, or hospitalization.[46]

One commonly used set of adjectives is dependent on the function of the output. In this instance, whether the model predicts the risk that a person has the health outcome or will develop the health outcome over a prespecified period of time warrants the addition of an adjective to the root term: *diagnostic* or *prognostic* prediction model.[30,33,56] The inclusion of either adjective can specify the temporal function of the model.

There exist a few terms that focus on the multivariable model created to derive the projected risk. These terms include risk *algorithm*, risk *function*, and risk *equation*, among others.[85–88] More attention is directed to the statistical relationship between the predictors and the outcome and how they can, in turn, generate a predicted risk. [52,89] These terms do not address the presentation of the model, such as whether the risk is presented in nomogram format or icon arrays, for example.

Conversely, terms pertaining to the presentation of the model exist as well. These terms include risk *chart*, risk *score*, risk *calculator*, risk *engine*, and *score cards*.[86,87,90,91,92] Risk charts and risk scores are both tools that simplify the derivation of absolute risk. Risk scores, as previously mentioned, are simplifications to the calculation of the patient's absolute risk, attributing points for each predictor, with the summed total points corresponding to the absolute risk of outcome.[67,71] Risk charts, conversely, simplify the process by providing a visual aid where absolute risk is presented based on the values of predictors.[86] Though they may both simplify the process, risk charts are absolute global risks derived from combinations of classes of risk factors, whilst risk scores are more precise evaluations derived from absolute global risks calculated by continuous levels of risk factors.[93] Risk scores can be depicted in a visual fashion through the use of score cards, which provide the score associated with absolute risk on individual cards with each card pertaining to a combination of classes of predictors.[94]

Risk calculators are tools that make risk prediction models accessible to broader audiences.[89] Risk prediction models at their core can be difficult to understand; the simplification of the model to a more user-friendly format can ease their implementation in practice. Risk calculators allow for healthcare providers to easily input the predictor values, automatically generating the estimated risk of outcome. In essence, they are standalone tools that can be electronic or paper-based.[95]

Risk engines are similar to risk calculators in terms of simplifying the calculation of risk. They are often used to describe a relationship through the use of technology, such as the development of mobile phone applications or web-based tools that calculate risk upon input of predictors.[96] One of the more prominent examples is the UKPDS Risk Engine, a model that predicts coronary heart disease amongst patients with type 2 diabetes, using a web-based automated calculation format.[97,98]

This series of terms is by no means exhaustive, but does provide an overview of the most commonly used terms. Despite the wide range of terms used in the field of prediction model research, they exist to describe the same basic tool with the same goal: to provide an accurate measure of risk of health outcome in patients based on the use of predictor

variables.[52] As such, a potentially more useful method of understanding prediction models is to provide an overarching classification under which models can be categorized.

2.5 Classifying risk prediction models according to their dominant characteristics

As previously seen, there exists numerous disparities in how researchers refer to risk prediction models. As such, it may be more useful to focus on a few key characteristics that define these tools rather than focusing on the terminology.

There are four primary ways that risk prediction models in present use can be classified (Figure 1). The classifications were selected because they encompass all existing prediction models in use. Note that the four peripheral nodes in the figure are not mutually exclusive of one another; rather, each risk prediction model can be classified according to one or more categories.

2.5.1 Temporality

All risk prediction models can be viewed through the lens of temporality. As previously described, they can be dichotomized as being prognostic or diagnostic, depending on whether the prediction is for a health outcome that is present or will occur in the future. Given that all risk prediction models calculate the risk for an outcome occurring, applying the concept of temporality on this outcome-dependent categorization provides an irrevocable measure of classification.

2.5.2 Type of outcome

Risk prediction models can also be classified according to the outcome for which they predict risk. Prediction models apply to several fields apart from medicine, including physics, meteorology, and astronomy.[30] When applied to medicine, they can be developed for several different health outcomes, including both acute and chronic conditions. One systematic review sought to synthesize all studies assessing the accuracy of tools predicting fracture risk, an acute outcome, such as the FRAX score, identifying 13 unique tools in 45 different studies that met their inclusion criteria.[99,100] Chronic

health outcomes, such as breast cancer, have been predicted quite extensively; one systematic review and meta-analysis identified 17 unique breast cancer models.[101] Indeed, given that all risk prediction models predict for at least one outcome, we can group models according to the nature of the outcome they seek to predict.

2.5.3 Setting of use

Risk prediction models can also, albeit to a lesser extent, depend on the setting of most appropriate implementation. Though many models apply to a primary care setting, such as most cardiovascular prediction models, a number apply to secondary and tertiary care settings.[24] For example, the miniPIERS risk prediction model is used in tertiary care settings to identify pregnant women at increased risk of death or complications due to hypertension.[102] Some overlap exists; the CHAD2 score, a prediction model assessing for risk of stroke, can be used in primary or tertiary care settings.[103] These tools may also be used in non-clinical settings. There is a growing trend towards publishing prediction models online, allowing members of the general public to calculate their risks of health outcome in the comfort of their own homes.[104] However, the models published online are typically less invasive and rely on more easily discernable risk factors, such as age or sex.

2.5.4 Format of presentation

Lastly, there are only a limited number of ways that clinicians can use a prediction model to ascertain the absolute risks of their patients. As such, the format of the risk prediction models can be used as another method of categorization. The two primary subgroups here would be whether the tool is used as either a paper- or electronic-based one. Within each group would fall the various specific risk prediction models, such as risk tables or charts, or risk engines, depending on the medium through which they are used. As such, one could see the most popular methods of delivery, allowing for the potential to determine if one is more effective than others.

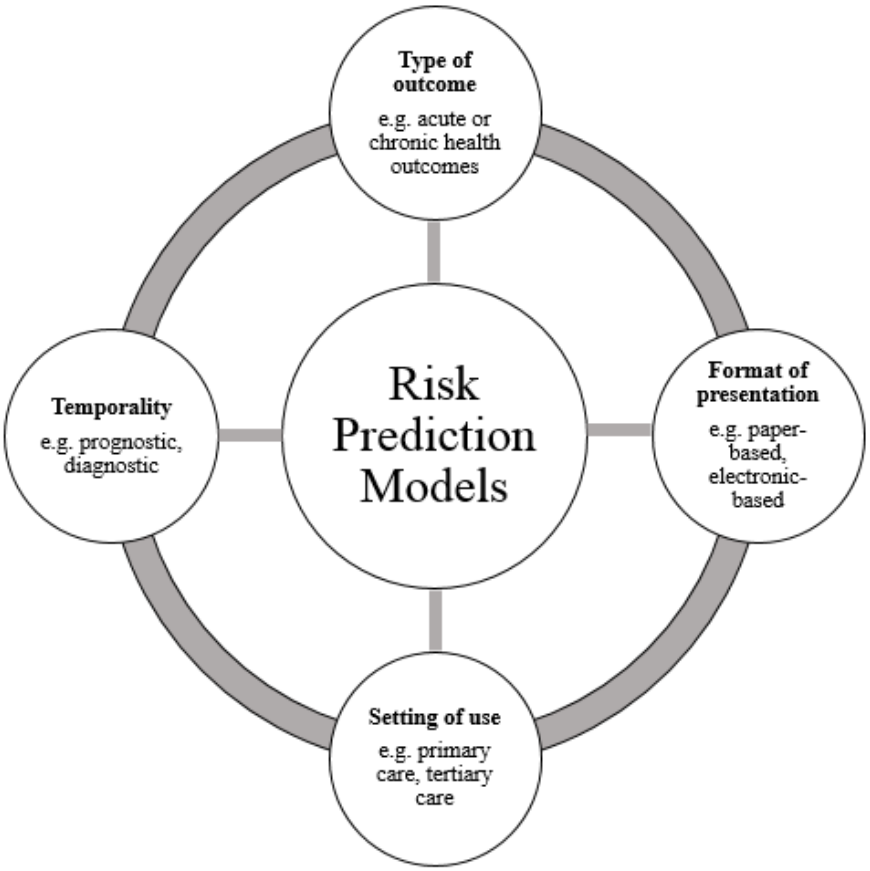

Figure 1. The four proposed methods of classifying risk prediction models.

2.6 Conclusion

Prediction models are becoming a common mainstay in clinical settings, being recommended by health policy makers and clinical guidelines globally. They provide an objective, evidence-based measure of patient risk of health outcome, and are capable of informing physicians and patients in making impartial judgements regarding patient management, potentially reducing the burden of disease faced by populations globally. Though the literature may be inconsistent in its terminology, agreement regarding the intended purpose of risk prediction models is consistent across studies, providing a strong basis for the independent examination of the impact of prediction models.

Chapter 3

3.0 Introduction

This chapter presents background information regarding chronic disease and the primary health care setting, particularly as they relate to the focus of this thesis. The literature regarding the role of risk prediction models in primary prevention, and more broadly in clinical practice, is explored. This is followed by a description of the rationale for the study as well as the study objectives.

This chapter explores the literature surrounding features associated with risk prediction models. It begins with an assessment of the term *chronic disease* as it has been used in the literature and for the purposes of the systematic review and meta-analysis. Next will be a description of *primary care settings*, the setting within which most preventative measures against chronic diseases are applied. Following is an exploration of the role of risk prediction models in terms of primary prevention, as well as reasons for their possible underuse in clinical practice. To close, the rationale for the study as well as the study objectives will be outlined.

3.1 Chronic disease

The burden of chronic diseases is vast and increasing rapidly globally. Though reporting differs dependent upon the source, it has been estimated that in 2001, of the 56.5 million total reported deaths, approximately 60% were attributed to chronic diseases, increasing to 68% in 2012.[4,105] By 2020, projections indicate that approximately 75% of deaths will be attributed to chronic diseases.[106] The reported prevalence amongst Canadians range from one in five to one in three living with a chronic disease, with up to four in five Canadians having at least one modifiable risk factor, such as tobacco smoking, poor diet, sedentary lifestyle, and harmful alcohol consumption.[4,5,107] Though a century ago, infectious diseases were the eminent causes of mortality, an epidemiologic transition has occurred in recent years, with chronic diseases dominating the landscape of illness worldwide.[108,109,110] Chronic diseases represent the largest cause of mortality nationally and internationally, a trend that will continue for the foreseeable future.

3.1.1 Chronic disease definitions

The term "chronic disease" is etymologically simple, with implications of temporality and of illness. However, there is lack of a consistent definition for chronic disease. Indeed, the lack of consistency in key definitions poses a barrier to the prevention and mitigation of any chronic condition, as it reduces the ability to measure them effectively.[111,112]

Researchers often create their own unique definitions to examine chronic diseases or chronic conditions. One study examining out-of-pocket expenditures for chronic disease management chose to define chronic *conditions* as, "…a person…having a chronic condition if that person's condition had lasted or was expected to last twelve or more months and resulted in functional limitations and/or the need for ongoing medical care."[113] To compile a list of specific chronic conditions, the researchers established a panel of ten physicians to judge whether the International Classification of Diseases, Ninth Revision (ICD-9) codes met their definition, resulting in 177 codes being classified as chronic conditions in adults.[113]

One systematic review sought to provide an overview of all definitions used for chronic conditions in children in an effort to establish the prevalence of chronic health conditions in that population.[114] The most frequently used terms were *chronic conditions, chronic health conditions, chronic illness*, and *special health care needs*. Four core definitions were identified, though not all included articles (64) adhered strictly to these (Table 3).

Table 3. Four most frequently used definitions of chronic conditions (for children). Adapted from van der Lee et al 2007.[114]

Source	Year	Term	Definition
Pless & Douglas[115]	1971	Chronic illness	"A physical, usually nonfatal condition that has lasted longer than 3 mo in a given year or necessitated a period of continuous hospitalization of more than 1 mo; of sufficient severity to interfere with the child's ordinary activities to some degree."
Perrin et al.[116]	1993	Chronic health conditions	"A condition is considered chronic if (1) it has lasted or is expected to last more than 3 mo and (2) the definition takes into account the impact of the condition on the child, e.g., level of functional impairment or medical need greater than expected for a child of that age."
Stein et al.[117]	1993	Chronic health conditions	"Conditions must have a biological, psychological, or cognitive basis; have lasted or are virtually certain to last for 1 y; and produce ≥ 1 of the following sequelae: (1) limitations of function, activities, or social role in comparison with healthy age peers in the general areas of physical, cognitive, emotional, and social growth and development; (2) dependency on 1 of the following to compensate for or minimize limitations of function, activities or social role: medications, special diet, medical technology, assistive device, or personal assistance; and (3) need for medical care or related services, psychological services, or educational services above the usual for the child's age or for special ongoing treatments, interventions, or accommodations at home or in school."
McPherson et al.[118]	1998	Children with special health care needs	"Children who have or are at increased risk of a chronic physical, developmental, behavioral, or emotional condition and who also require health care and related services of a type or amount beyond that required by children generally."

Of particular interest is the change in definitions presented over time, demonstrating the plasticity of the definition and its non-uniform use over time and amongst researchers. The earliest definition devised in 1971 addressed longevity and its impact on daily activities, with later definitions addressing the child's health care needs and functioning, as well as eventually addressing children at risk for conditions.[115,116,117,118]

Medicare, the largest health insurance program in the United States, has established their own categorizations of diseases. Medicare provides health insurance to approximately 40 million beneficiaries amounting to an annual spending exceeding 200 billion USD, placing an enormous financial responsibility on Medicare managed care and other capitated programs.[119] To ensure the appropriate allocation of benefits, a health-based Medicare capitation system was adopted creating a diagnostic classification system.[119] This system aggregated over 15,000 ICD-CM codes (International Classification of Diseases, Ninth Revision, Clinical Modification) into 70 Hierarchical Condition Categories (HCC). For example, the HCC "Acute Liver Failure/Disease" includes the ICD codes for "Viral Hepatitis, Acute or Unspecified" and "Hepatic Coma".[119]

The Centers for Disease Control and Prevention also compiled a list of select definitions of chronic diseases representing the definitions used in settings including academia and the government (Table 4).[111]

Table 4. List of commonly used definitions for chronic diseases. Adapted from Goodman et al 2013.[111]

Source	Year	Definition
Hwang et al.[113]	2001	"We defined a person as having a chronic condition if that person's condition had lasted or was expected to last 12 or more months and resulted in functional limitations and/or the need for ongoing medical care."
Bernstein et al.[120]	2003	"A chronic disease or condition has 1 or more of the following characteristics: is permanent; leaves residual disability; is caused by nonreversible pathological alteration; requires special training of the patient for rehabilitation; or may be expected to require a long period of supervision, observation, or care."
Friedman et al.[121]	2008	*"Chronic condition* is defined as a condition that lasts 12 months or longer and meets 1 or both of the following tests: 1) it places limitations on self-care, independent living, and social interactions; and 2) it results in the need for ongoing intervention with medical products, services, and special equipment."
National Center for Health Statistics[122]	2011	"A health condition is a departure from a state of physical or mental well-being. In the National Health Interview Survey, each condition reported as a cause of an individual's activity limitation has been classified as chronic, not chronic, or unknown if chronic, based on the nature and duration of the condition. Conditions that are not cured once acquired (such as heart disease, diabetes, and birth defects in the original response categories, and amputee and old age in the ad hoc categories) are considered chronic, whereas conditions related to pregnancy are not considered chronic. Other conditions must have been present for 3 months or longer to be considered chronic."
McKenna and Collins[123]	2010	"They are generally characterized by uncertain etiology, multiple risk factors, a long latency period, a prolonged course of illness, noncontagious origin, functional impairment or disability, and incurability."
World Health Organization[3]	2017	"Noncommunicable diseases, also known as chronic diseases, are not passed from person to person. They are of long duration and generally slow progression."

Universal within these definitions are the concept of longevity, ranging from greater than three months to greater than twelve months to a permanent affliction. Some incorporate aspects of impairment, others mention the need for ongoing medical care, whilst others still place emphasis on communicability, or rather, lack thereof. Some of these concepts are in contradiction with one another. For example, human immunodeficiency virus (HIV) infection has in recent years, due to the advent and introduction of combination antiretroviral (ART) therapy, prolonged life in HIV-infected patients by a measure of decades.[124] As such, due to its lengthy duration and the need for medical products (ART therapy), it would meet the Friedman definition of chronic diseases.[121] However, due to its certain etiology and its contagious origin, it would fail to meet the McKenna and Collins definition.[123] In other words, there exists no consistent universal definition of what comprises a chronic disease.

3.1.2 Chronic disease definition used in thesis

In recognition of this lack of consistency, a different approach was chosen for this systematic review. Rather than taking an approach similar to Hwang et al.[113], for example, where potential chronic diseases were vetted by physicians, this systematic review chose to focus on overarching categorizations of chronic diseases. The method used by Hwang et al. takes a top-down approach where characteristics of what constitute a chronic disease are applied to specific diseases in order to decide amongst a panel of individuals whether they are classified as chronic. This process is prone to bias and is time-consuming given the enormity of conditions or diseases that may be considered chronic. Instead, the World Health Organization (WHO) categories of chronic disease were used herein.

The WHO recognizes four main types of chronic diseases (referred to as noncommunicable diseases, or NCDs, by the WHO), which are: 1) cardiovascular diseases, 2) cancers, 3) chronic respiratory diseases, and 4) diabetes.[125] In 2012, 56 million deaths occurred globally, with 38 million of those as a result of NCDs; 82% of these were attributed to the four aforementioned NCDs.[126] The broadness of these categories, their large rates of morbidity and mortality, and the fact that they make up a

sizable majority of diseases, make this system of classification more feasible and practical for the conduct of this systematic review.

3.1.3 How does risk prediction modelling apply to chronic diseases?

Previously when the types of diseases that affected populations were of a primarily infectious nature, such as diarrheal diseases, applicable risk factors, commonly referred to as "traditional risks", were undernutrition, unsafe sex, unsafe water, poor sanitation and hygiene, and indoor smoke, and were often associated with low-income populations.[109] However, with the epidemiologic shift towards chronic diseases and away from communicable diseases, there has been a corresponding shift in the prevalence of different risk factors.[127] The leading global risks for chronic diseases are high blood pressure, tobacco use, alcohol use, high blood glucose, physical inactivity, high cholesterol, and overweight/obesity.[109,127,128]

As a relatively small number of risk factors can cause or are predictive of several chronic diseases, and may interact in their impact on the risk of disease, the attributable risk of individual risk factors add up to more than 100%.[109] Otherwise, the assumption would be that each case of disease has but a single cause, and that multiple risk factors cannot cause the same case of disease.[109,129] This makes it difficult to quantify the impact of single risk factors on an individual's absolute risk of disease. This lends credence to the concept of targeting the absolute risk of chronic disease for intervention as opposed to individual risk factor levels.[22,130,131] Risk prediction models account for the additive and interactive effects of predictors, where they exist, on the absolute risk of disease, providing an objective measure for physicians and patients to target for intervention.[45,132]

For example, the Harvard Cancer Risk Index assesses for a person's risk of 12 forms of cancer, including lung, breast, and colon cancer.[133] Epidemiologic investigation revealed a set of risk factors, including: sex, age, height, weight, medication use, medical history, diet, physical activity, family history, and prior screening. Using this knowledge of the effects of risk factors and their synergistic effect, an objective measure of cancer risk can be determined, allowing for multitargeted interventions to reduce the absolute risk.[133]

These known relationships between both modifiable and non-modifiable risk factors allow for the prediction of the development of chronic diseases in individuals.

3.2 Primary care settings

The Declaration of Alma-Ata of 1978, adopted at the International Conference on Primary Health Care, stated the goal of the WHO and United Nations was to achieve, "Health for All by 2000," positioning primary health care as the strategy to achieve their goal.[134,135] The role of primary health care was to ensure equitable provisions of quality health services to all persons in an efficient, sustainable, and universal manner.[135] It was considered the most effective strategy to ensure health for all was obtainable, and was grounded upon a set of principles including universal access, addresses the movement toward health equity, and the intersectoral approach to health.[134,136] However, despite primary care taking the foremost role in achieving equitable global health, dependent upon the setting, it can stand to mean something quite different. For instance, in areas with higher levels of healthcare accessibility (i.e. high- and middle-income countries), primary health care can be viewed as the first level of care; conversely, where challenges in accessibility are highly prevalent (i.e. low-income countries), it can be viewed as a system-wide approach.[136]

It can thus be useful to view primary care as a set of activities as well as a set of principles. In terms of the activities engaged within primary care are the delivery of first-contact medicine, the assumption of longitudinal responsibility by practitioners for the patient, as well as responsibility of *health* (defined as the complete physical, mental and social wellbeing and not merely the absence of disease or infirmity) within the limits of health personnel.[136,137] Primary care can be condensed to its four essential components: first contact, longitudinality, comprehensiveness, and coordination.[137]

3.2.1 Primary care as an avenue for prevention

The functions of primary care are enormous, providing a wide spectrum of services ranging from acute and chronic health care to preventive care and health promotion.[138] As the point of first contact for patients with the health care system, primary care seeks to

coordinate use of other levels of care (secondary and tertiary, respectively), making arrangements with specialists where necessary.[137,138] The varying levels of care represent different functions; where primary care physicians, for example, are considered generalists, resource and knowledge constraints may necessitate a referral to a specialist with a higher degree of skill in a particular area of medicine.[137]

On the other hand, specialized care often receives "sicker" patients, and thus the emphasis of care is to sustain life in the ill individual.[137] As such, little emphasis is placed on the prevention of disease onset in specialist settings, while comparatively, a greater amount of energy is dedicated to the prevention of illness in primary care.[137,139] As such, the primary care physician plays an integral role in the prevention of disease.[34]

Continuity of care, or longitudinality, is more likely to occur in primary care settings, which has been associated with a greater use of preventive services, compared to different subspecialty practices, which see more first-time patients.[137,140,141,142] Indeed, in one study examining factors associated with preventive services, having a regular place of care was most associated with receipt of preventive care when adjusted for demographic and financial characteristics as well as health status.[140] A larger percentage of visits to primary care practices are related to prevention when compared to more specialized care.[137] As a result of its very nature, primary care settings are well established to help prevent the onset of chronic disease.

3.3 Risk prediction models as a tool for prevention

Risk prediction models have the potential to play an integral role in prevention. Within the constructs of public health and healthcare in general, prevention is often segmented as either primary, secondary, or tertiary prevention, categorizations that pertain to the state of disease or injury. Secondary and tertiary prevention aim to reduce the impact of disease or injury either early in its course (secondary) or when it is already established (tertiary).[143] Conversely, primary prevention aims to prevent disease or injury in healthy individuals.[143,144]

Two options exist when addressing primary prevention: 1) the "population-based" approach, where preventive actions are generally applied to groups of people, and 2) the "high risk" approach, where interventions are targeted to those at highest risk of developing the outcome.[145,146] Primary prevention in a healthcare setting seeks to identify high risk individuals, thereby allowing the targeting of interventions to those who would benefit greatest.[93,147] Given the limited preventive resources available, taking a high risk approach and allocating those resources to high risk individuals can potentially enable the greatest reduction in adverse events for patients treated in primary care.[148] This can provide a complement to a public health approach where interventions are generally 'targeted' to the population.[149]

Due to the enormous burden of disease-related morbidity and mortality associated with chronic diseases, their primary prevention is of high importance.[150,151] As the patient's medical "home", primary care is well-positioned to prevent the onset of these diseases through the provision of evidence-based preventive care.[147,152] Though time constraints reduce the ability of primary care physicians to recommended preventive services to their patients, within the present construct of medical care, primary care settings still play an important role in primary prevention.[153] Indeed, numerous national guidelines suggest implementation of preventive services in primary care. The National Health Service in the United Kingdom, for example, recommends that primary prevention for CVD occur in primary care.[154]

The interventions employed in primary care settings for the primary prevention of chronic diseases should be cost-effective, practical, possible, and positively affect risk status and outcomes.[155] For example, tobacco cessation can be promoted through brief counselling and cessation advice, which may result in a lifestyle modification, ultimately reducing the patient's risk of several chronic diseases.[155,156] Pharmacotherapy may indicated for the prevention of cardiovascular disease and type 2 diabetes.[155,157] Any number of interventions may be used in primary care settings dependent upon the resources available and the disease outcome of interest.

Numerous guidelines have been published with the goal of preventing the onset of chronic diseases. Several of these recommend the usage of risk prediction models to predict patients' absolute risk of developing chronic diseases. Guidelines published by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, the American Heart Association (AHA) in the United States, the New Zealand Guidelines Group (NZGG) in New Zealand, and the Canadian Cardiovascular Society (CCS) in Canada, amongst several others, each recommend the assessment of absolute cardiovascular risk using a risk prediction model.[158,159,160,161] Given that these tools can stratify patients, determining who is at greatest risk for chronic disease, they can provide appropriate and objective guidance to assist in the prevention of disease.

3.4 Intended effects and explanations

Despite the numerous recommendations to incorporate risk prediction models in clinical practice, few studies have assessed whether they have an effect.[78,162] Risk prediction models are intended to guide clinical decision-making and patient management, such as conducting additional testing, issuing prescriptions, as well as informing patients of their risk of outcome.[48] They are not intended to replace physicians, but to complement and assist their clinical judgment.[48,163] When appropriately applied and interpreted, physician judgement of clinical information can be made more accurate and efficient.[164] The Evidence-Based Medicine Working Group stated that risk prediction models can, "…change clinical behavior and reduce unnecessary costs while maintaining quality of care and patient satisfaction."[162]

Risk prediction models provide an absolute measure of risk for outcomes. In doing so, they reduce the amount of uncertainty faced in medical practice by making apparent and evident the impact of clinical findings on long-term risk.[164] This is in contrast to the use of clinical experience, whereby intuition, a more subjective method of evaluation, is the final arbiter of medical decision-making.[162] Though clinical judgment through use of heuristics may sometimes provide an accurate measure of absolute risk, statistical models are capable of integrating data quickly and accurately, providing an objective measure.[165]

The implementation of risk prediction models can assist in shared decision-making. Shared decision-making is defined as: "…an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences."[166] Risk prediction models can be used as shared decision-making tools. Shared decision making tools are intended to foster a consideration of the risk, benefits, and trade-offs associated with a decision, and the way in which a patient's preferences are incorporated into the discussion and decision process.[167,168] In this fashion, there can be improvements in risk communication and objective discussions between physician and patient, allowing patients to participate informedly in shared decision-making.[169]

The information provided to patients by physician and model can improve risk perception, and with increased risk perception, there is the possibility of associated behaviour change. The 'teachable moment', an event or circumstances leading persons to alter their behaviour, can promote health behaviour change in numerous settings.[170] Medical procedures, such as cancer screening, have been posited to constitute a teachable moment.[171] Teachable moments may also be created by physicians rather than waiting for an unpredictable opportunity, leading to patient activation, or instilling in patients the knowledge, skills, and confidence to effectively manage their health.[172,173] Though analogous, the provision of personalized risk estimates may constitute a teachable moment, providing patients with the knowledge associated with their health thereby improving their risk perception. In this fashion, patients may thus feel more confident in their ability to improve their long-term risk of disease.

3.5 Barriers to model usage in clinical practice

Though model usage in clinical practice is often recommended in clinical guidelines, evidence suggests that practitioners often do not adhere to guideline recommendations. One study of Belgian general practitioners found that 53% of participants reported having never used a tool for global cardiovascular risk assessment, with 80% of participants erroneously believing total cholesterol is an accurate proxy for cardiovascular risk.[174] Further, it has been noted that physicians often take poor account of increasing age and

other risk factors, indicating there is a need for models to help in the assessment of risk.[175]

Numerous reasons have been given for why models are not used in clinical practice. Some physicians experience a lack of belief in the risk estimates, fearing that they do not account for other factors that are crucial, while others believe they are more capable of estimating the global risk without the model.[176] Some physicians believe models overpredict CVD risk because of these models were developed using older data.[177,178] One study examined automated prompts to conduct risk assessments, which led to what they referred to as "prompt fatigue", or a form of clinical inertia where physicians failed or refused to answer computerized prompts despite recommendations to do so.[179]

Others still cite a lack of time or lack of physician knowledge and training as key reasons for their lack of use.[180] It is possible that the use of educational interventions targeted at physicians could increase the uptake of risk prediction models in clinical settings. One study examining the impact of a continual medical education session training general practitioners on the use of global cardiovascular risk found that trained physicians used a tool to assess risk more often than untrained physicians (76% vs. 52%).[181]

Even with the use of risk prediction models, adherence to treatment guidelines based on risk stratification remains poor. One examination of the CHA2DS2VASc tool, a model predicting the risk of stroke in patients with atrial fibrillation, found that low-risk patients were being treated with warfarin, an anticoagulant, despite a lack of evidence regarding its clinical benefit.[182] The misinterpretation of generated outputs from risk prediction models may be to blame, with some studies demonstrating that physicians experience some difficulties with statistical concepts.[183]

The presentation of risk may or may not have an impact on outcomes. For example, one study conducted in the United Kingdom assessed for changes in prescribing patterns and changes in risk factor levels following the presentation of risk as either an absolute risk level or a number needed to treat, and found no differences between the two groups.[184] Some clinicians have called for the number needed to treat (NNT) to be presented as well

to improve the dialogue between physician and patient, though they recognized that individual patients may not understand the concept.[177]

Several barriers exist preventing the uptake of risk prediction models in clinical practice. Though these factors are not necessarily insurmountable, they provide a greater understanding of the issues faced by physicians when presented with novel tools for use, as well as areas for interventions to increase their uptake.

3.6 Study rationale and objectives

There is a growing body of literature surrounding risk prediction models. Though a negligible number of studies with the terms 'prognostic model' or 'prediction model' were found dating from the 1970s and 1980s, an exponential increase has occurred in recent years, with well over half a million studies identified in the year 2005.[30] This increase in literature parallels the growing movement towards evidence-based medicine and the corresponding incorporation of risk prediction models in clinical guidelines.[34,96,185] Further, the Cochrane Collaboration has recently developed reporting guidelines for prediction modelling studies, which could help shape the conduct of future research and reporting.[60]

However, a lack of evidence and poor reporting remain prevalent in the realm of prediction model research.[12,186] Despite numerous tools being available, few are used in clinical practice, indicating physicians may lack confidence regarding model usage for preventive patient management.[186] Though risk prediction models have been recommended for use in clinical practice by several guidelines to calculate the absolute risk of several chronic health outcomes, it has been suggested that physicians fail to use them consistently when indicated. Their implementation and use should help guide physician's behaviour, thus affecting patient behaviour, and ultimately showing an improvement in patient health outcomes.[187]

The recent paradigm shift towards evidence-based medicine provides one potential reason for their underuse. Clinicians are recommended to evaluate the weight of the evidence from which the guidelines are derived in keeping with the tenets of evidence-

based medicine, and to examine whether the incorporation of models can affect a positive change. At present, few impact analysis studies have been conducted, with no consensus amongst clinicians and researchers regarding the impact of model use.[188]

Therefore, the objective of this study was to: conduct a systematic review and meta-analysis to assess whether or not risk prediction model use in primary care settings can positively influence the prevention of chronic diseases. The study research question was: What is the impact of chronic disease risk prediction model use in primary care settings on: 1) physician behaviour, 2) patient behaviour, and 3) patient health outcomes?

In conducting this systematic review and answering the research question, uncertainties regarding the third domain of risk prediction model research, or assessing the impact of model use, would be addressed. Though a tremendous number of models for several outcomes have been developed, the literature remains unclear regarding the impact of model use on clinical practice. Answering this knowledge gap will help to inform the future use and implementation of models, and may ultimately help to reduce the global burden of chronic disease.

Chapter 4

4.0 Methods

This chapter provides a detailed account of the steps undertaken in the conduct of the systematic review and meta-analysis. The presented research study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines, and the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS Checklist), developed by the Cochrane Collaboration Prognosis Reviews Methods Group.[60,189]

A systematic review aims to provide an unbiased answer to a specific research question by collecting and synthesizing all evidence presently available in the literature that meet an a priori specified eligibility criteria.[190] This review seeks to answer: what is the impact of chronic disease risk prediction models on physician behaviour, patient behaviour, and patient health outcomes? Addressing the components of checklists such as PRISMA allows for the reproducibility of the review by providing an explicit, transparent methodology, including but not limited to the systematic search of the literature, or assessments of the validity of findings through means such as a risk of bias tool.[190] Where possible, a meta-analysis may be conducted, which is a statistical summary of the results of independent studies, therefore producing a more precise summary estimate of the impact of healthcare interventions.[190] The generation of figures such as forest plots may allow readers to examine the consistency of the evidence and provide insight into the differences between studies.

4.1 Search strategy

A search strategy was iteratively created in consultation with a research librarian. Search terms were developed for the following databases: MEDLINE, Embase, the Cochrane Library, CINAHL, and Web of Science. Additional e-sources were searched for grey literature, specifically The Canadian Agency for Drugs and Technologies in Health (CADTH), OpenGrey.eu, and ClinicalTrials.gov. Medical subject headings (MeSH),

where applicable, and keywords were tailored to each database to ensure the comprehensiveness of the search. The search was restricted to publications from 1976 to 2017, those in the English language, and those assessing human subjects. Four primary concepts pertaining to the PICOS, or the types of Participants, the Intervention and Comparison, the Outcomes, and Study design, of the research question to inform the search strategy, specifically: 1) risk, 2) prediction model, 3) chronic disease, and 4) primary care setting. The search terms used for the three databases using MeSH terms or subject headings are included below in Table 5.

Table 5. MeSH terms and keywords used for Medline, Embase, and CINAHL.

Concept	Medline	Embase	CINAHL	Keywords
Risk	Risk/ OR Risk Factors/ OR Risk Adjustment/	Risk/ OR Patient Risk/ OR Expectancy/ OR Risk Factor/	(MH "Risk Factors+") OR (MH "Health Screening+") OR (MH "Patient Assessment+")	Risk adj3 (adjust* OR factor*) OR Probabilit* OR Likelihood
Prediction models	Technology Assessment, Biomedical/ OR Algorithms/ OR Probability/ OR Bayes Theorem/ OR Likelihood Functions/ OR Proportional Hazards Models/ OR "Sensitivity and Specificity"/ OR ROC Curve/ OR exp Decision Support Techniques/ OR Area Under Curve/ OR Clinical Decision-Making/ OR exp Risk Assessment/	Cardiometabolic Risk/ OR Cardiovascular Risk/ OR Coronary Risk/ OR Probability/ OR Reynolds risk score/ OR Framingham risk score/ OR CHADS2 Score/ OR Cardiovascular Disease Assessment/ OR PROCAM Score/ OR QRISK Score/ OR Multiple Regression/ OR Receiver Operating Characteristic/ OR exp Area Under the Curve/ OR exp "prediction and	(MH "Predictive Value of Tests") OR (MH "Predictive Research") OR (MH "Models, Statistical") OR (MH "Decision Support Techniques+") OR (MH "Decision Making, Clinical") OR (MH "Clinical Assessment Tools") OR (MH "Risk Assessment") OR (MH "ROC Curve") OR (MH "Regression+") OR (MH "Survival Analysis+")	"Risk scor*" OR risk tool* OR risk estimat* OR risk assess* OR risk function* OR risk equation* OR risk calc* OR risk scor* OR risk predict* OR risk factor calc* OR risk chart* OR risk engine* OR risk appraisal* OR prediction model* OR risk algorithm* OR scoring* method* OR scoring scheme* OR roc curve OR area under curve OR AUC

		forecasting"/ OR survival prediction/ OR survival rate/ OR exp decision support system/ OR clinical decision making/ OR medical decision making/ OR medical assessment/		OR c-statistic* OR C index* OR C indices* OR hazard ratio
Chronic disease	Chronic Disease/ OR Cardiovascular Diseases/ OR exp Heart Diseases/ OR exp Vascular Diseases/ OR exp Lung Diseases, Obstructive/ OR Diabetes Mellitus/ OR Diabetes Mellitus, Type 1/ OR exp Diabetes Mellitus, Type 2/	Chronic Disease/ OR Cardiovascular Disease/ OR Heart Disease/ OR Vascular Disease/ OR Lung Disease/ OR Chronic Lung Disease/ OR Chronic Obstructive Lung Disease/ OR Asthma/ OR Diabetes Mellitus/ OR Insulin Dependent Diabetes Mellitus/ OR Non Insulin Dependent Diabetes Mellitus/	(MH "Chronic Disease") OR (MH "Cardiovascular Diseases") OR (MH "Heart Diseases") OR (MH "Vascular Diseases") OR (MH "Lung Diseases") OR (MH "Lung Diseases, Obstructive+") OR (MH "Diabetes Mellitus") OR (MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2")	Chronic disease* OR Chronic illness* OR chronically ill OR non-communicable disease* OR cardiovascular disease* OR vascular disease* OR heart disease* OR stroke OR respiratory disease* OR asthma OR COPD OR chronic obstructive pulmonary disease* OR diabetes OR diabetes mellitus OR diabetic
Primary care	Primary Health Care/ OR Comprehensive Health Care/ OR Continuity of Patient Care/ OR Patient-Centered Care/ OR exp General Practice/	Exp Primary Health Care/ OR General Practice/	(MH "Primary Health Care") OR (MH "Family Centered Care+")	Primary health care OR primary care OR primary healthcare OR primary medical care OR family practice OR family medicine OR general practi*

To ensure the completeness of the search, backward and forward searching was conducted, whereby backward searching was conducted through examination of included articles' bibliographies, and forward searching was conducted through use of Google Scholar to determine where the article had been cited in the literature. Forward and backward searching provides an additional opportunity to identify studies that fulfill the eligibility criteria of the review that may not have been captured in the initial search.

4.2 Eligibility criteria

The eligibility criteria through which articles were screening (section 5.3) were selected to align with the objectives of the study by identifying the key components associated with the research question through adaptation of the PICOS framework.

4.2.1 Participants

There are two main groups of participants associated with the research question: physicians and patients. The physician population applicable to the research question were those practicing in primary care settings, which generally refers to family physicians or general physicians. A preliminary search found that the type of physician was not consistently specified in studies, so the criterion was expanded to include the primary care setting. Specifically, a primary care setting was defined as the first point of contact for patients into the health care system, and includes rural and urban general practice clinics, either group or solo physician practices, as well as community-based programs.

The second group of participants are the patients. Patients were not restricted by any demographic characteristic, such as age or sex. Patients were required to be asymptomatic for the disease outcome of interest at study intake, however, because to assess a patient presenting with symptoms of the disease outcome for the risk of developing the disease is unlikely when compared to alternative measures, such as the conduct of diagnostic testing. Of most importance is that patients assessed were appropriate for the prediction model assessed in each study.

4.2.2 Intervention

The present study aims to assess the impact of risk prediction models, specifically the provision of long-term risk of health outcomes as a result of risk prediction model use. The intervention was restricted to prognostic—not diagnostic—models that predict for the long-term risk of a chronic disease. The chronic diseases of interest were those that fall under the four main categories of NCDs as per the WHO: CVD, cancers, diabetes, and chronic lung diseases. Though there are several models that are diagnostic or assess for non-chronic health outcomes, they were excluded in this systematic review. Therefore, models assessing for the risk of behavioural, mental, or acute health outcome, such as risk of sexually transmitted infections, risk of schizophrenia, or risk of fracture, were excluded. The comparison group were patients who were treated without risk prediction models.

4.2.3 Outcome

Three outcomes were assessed: 1) physician behaviour, 2) patient behaviour, and 3) patient health outcomes.

1) Physician behaviour: any study that evaluated the impact of physician use of a risk prediction model on either behavioural outcomes or health outcomes was considered. The specific types of outcomes of interest were those with the potential to impact the patient's risk of developing a chronic disease. Therefore, physician behaviours of interest include prescribing behaviours, provision of lifestyle or dietary counselling, and referrals to specialists or other healthcare providers.
2) Patient behaviour: behaviours of interest include fulfilment or dispensing of prescriptions, medication adherence, lifestyle changes such as smoking cessation, and dietary changes.
3) 3) Patient health outcomes: these outcomes were defined as risk factor levels, absolute risk of disease, and event rates.

Though examples of each outcome are provided, the examples only provided a measure of guidance. Given the sparsity of studies assessing model impact and the differences in methodology, specific outcomes not previously stated were independently assessed to determine their eligibility to be classified as one of the three outcomes.

4.2.4 Study design

All study designs were considered including experimental, observational, and qualitative designs. For experimental and observational studies, the design was considered appropriate only if it contained a comparison group to provide a measure of risk difference attributable to the intervention. Therefore, case studies and narrative reviews were excluded. Pre-post studies were included for data synthesis as per the systematic review, but were not considered appropriate for meta-analysis due to the lack of a control group. Pre-post studies are used to demonstrate causality between an intervention and an outcome; however, they are prone to errors such as regression to the mean or confounding.[191] Further, as per the statistical analysis plan (Section 4.5), the effect sizes are generated by comparing the absolute change from baseline to follow-up between the intervention and control group, allowing the final effect size to represent both the direction *and* magnitude of effect. Studies were restricted to those published on or after 1976, the year the first prediction model was published.[13] No geographic restrictions were placed on the location of studies to ensure comprehensiveness of the search.

4.3 Screening

Citations identified from the search were imported into Covidence, a systematic review software, which automatically eliminated duplicated articles, followed by a manual search for duplicates.[192] Two levels of screening were employed to identify studies that met the prespecified eligibility criteria. The first level of screening was conducted by two reviewers (PK, JB) independently through an assessment of the titles and abstracts of the citations. Once the title/abstract screening was completed by both reviewers, disagreements were reconciled through discussion of each conflict, with any unresolved articles being reviewed by a third party (DL) to reach consensus. Studies that proceeded to the second level screening were reviewed by two reviewers (PK, KN), who first

conducted a pilot of 15 articles to ensure reliability, then completed the screening of full-text articles with conflict resolution occurring upon completion. Any irreconcilable conflicts were resolved by a third party (DL). The specific criteria by which articles were screened derived from the eligibility criteria are listed in Appendix C.

4.4 Data extraction

Data were extracted from the complete list of included articles using a form based on the Cochrane Consumers and Communication template.[193] The Cochrane template recommends that data be extracted according to seven categories: 1) general review information, 2) methods of the study, 3) risk of bias assessment, 4) study characteristics – participants, 5) study characteristics – interventions and comparisons, 6) study characteristics – outcomes, and 7) data and results.[193] The risk of bias assessment step was conducted using an independent tool as the Cochrane template outlines bias assessment items that are not applicable to observational studies. The data extraction form was tested using three of the included studies. A panel of researchers reviewed the results to ensure the comprehensiveness and appropriateness of the form. The form was amended based on this feedback. Subsequently, data were extracted by one reviewer (PK) from all the included studies using this form.

4.4.1 Items extracted

Items were extracted based on the seven categories outlined in the Cochrane template.

1) General review information: To identify the article and associated study. Items extracted were DOI, author(s), year of publication, country, and name of study where applicable.
2) Methods of study: To determine what methodology was employed per each study. Items extracted for the methods of the study category included study objective(s), study setting, and study design.
3) Risk of bias assessment: Data were not extracted specifically for risk of bias assessment as a separate risk of bias assessment tool was used.

4) Study characteristics were divided into three categories: participants, interventions and comparisons, and outcomes.
    a. Participants: Items extracted pertaining to the participants and interventions were participant demographics including age and sex, as well as all numbers pertaining to participants (e.g. number of participants recruited, number of participants lost to follow-up).
    b. Interventions and comparisons: Items extracted included the name of prediction model used, health outcome of model, a brief description of the intervention as well as any procedures in addition of the provision of projected risk (e.g. dietary counseling, lifestyle recommendations).
    c. Outcomes: The outcomes extracted were categorized into physician behaviour, patient behaviour, and patient health outcomes. Both qualitative and quantitative data were extracted. Information pertaining to methods of outcome assessment (e.g. survey, face-to-face), methods of follow-up, and frequency and length of follow-up were also recorded.
5) Data and results: Items extracted were dependent upon study design, though generally provided the absolute numbers as opposed to relative measures where possible to allow for accurate comparisons between studies in addition to mean differences and standard deviations, where reported. For example, where an outcome assessed for changes in systolic blood pressure, dependent on study design, baseline and follow-up blood pressure in the intervention and control group were recorded, in addition to standard deviations. Where available, absolute changes in blood pressure with the corresponding standard deviation were recorded. In the case of dichotomous outcomes, number of baseline and follow-up events in both the intervention and control group were recorded in place of risk or odds ratios. Further, where applicable, qualitative themes were recorded in the data extraction form with notations denoting their location in the original article.

4.5 Statistical analysis plan

A meta-analysis was conducted to allow for the statistical synthesis of outcome data presented in the identified studies. At its core, a meta-analysis is a statistical process whereby the effect sizes of two or more studies may be combined, creating a summary effect measure.[194] This process is supported by *weighting* studies by placing greater importance or impact on the summary effect on studies with relatively good precision.[194] The analysis was completed using Stata v. 14.[195]

Firstly, the number of studies reporting on the same outcome measure was tallied; where two or more studies reported on the same outcome, they were explored for numeric similarities, which would allow for the calculation of a summary effect measure. When conducting a meta-analysis for dichotomous data, the number of events and non-events are required in order to calculate a measure of effect, such as an odds ratio or relative risk. For continuous data, for each group, the sample size, mean value, and standard deviation are required to calculate the standardized mean difference.

Where only proportions of binary data were reported, the number of new events was calculated by subtracting the follow-up number of events from the baseline, while the number of non-events was calculated by subtracting the total number of participants by the number of new events. For continuous outcomes, where only baseline and follow-up mean values were provided, with no measure of absolute change reported, it was calculated by subtracting the follow-up value from the baseline value. The standard deviation of the absolute change was calculated by imputing a correlation coefficient value derived from studies reporting absolute changes in the continuous outcome into equations provided by the Cochrane Handbook for Systematic Reviews of Interventions and Borenstein et al.[190,194]

The calculated data were then inputted in Stata. For binary data, the two-by-two contingency tables of each study were generated, whereas for continuous data, the calculated sample sizes, means, and standard deviations of the absolute change were imported. Using the metan function, forest plots, a visual representation of the magnitude

and direction of effect, were generated, as well as measures of uncertainty (i.e. 95% confidence intervals).

For the binary data, the odds ratio was selected as the measure of effect. The designs of studies included for meta-analysis were varied, and included case-control studies, where the prevalence of the outcome of interest was artefactually created. Relative risks are only appropriate where the *true* prevalence can be calculated, while odds ratios are robust to fabricated prevalence rates, hence their selection to calculate a summary effect measure.[190]

The calculation of a summary effect measure requires a distinction between fixed- and random-effect models. Fixed-effect models assume that there is one true effect size across all studies in the analysis, and that any differences between studies in terms of observed effect is attributable to sampling error.[194] The random-effect model, conversely, assumes that the observed effect differs across included studies, and aims to estimate the *mean* of this distribution.[194] Fixed-effect models are generally considered appropriate if all studies are essentially identical; however, the studies included for analysis, though similar in terms of outcome, were performed in independence of one another on varying populations, and thus an assumption of a true or common effect size would be inappropriate.[194] Therefore, a random-effect model was used to conduct the meta-analysis to account for the heterogeneity between studies.

4.6 Risk of bias assessment

A risk of bias assessment was conducted using the Downs and Black tool, and checklist assessing the methodological quality of randomized and non-randomized studies.[196] The Downs and Black tool consists of 27 items assessing the quality of five domains: 1) reporting, 2) external validity, 3) bias, 4) confounding, and 5) power.[196] The completion of the checklist allows for the calculation of an overall, composite score for study quality, but also scores for each of the five aforementioned domains.

The Downs and Black tool is one of the most commonly used numerical rating scales with frequent application in systematic reviews, and is well-validated with a high degree

of interrater reliability.[197,198] Further, it is one of the few tools capable of assessing the risk of bias of both randomized and non-randomized studies.[197] Therefore, the Downs and Black tool was selected to assess the risk of bias for studies included in this systematic review.

The checklist was used for each of the 22 included studies. A cumulative summary score was calculated by averaging the total scores derived from the checklist for each study. However, a summary score is discouraged by the Cochrane Handbook, as it differentially assigns a weight to different aspects of the checklist.[190] Hence, a bar graph was constructed to demonstrate the risk of bias in each domain.

Chapter 5

5.0 Results

Presented in this chapter are the results of the systematic review and meta-analysis. It begins by describing the results of the study selection process, and the characteristics of the included studies. The results of the individual studies are then assessed as per their outcomes in alignment with the study objectives in the form of a qualitative synthesis and the meta-analysis. Lastly, the risk of bias assessment is also presented.

5.1 Study selection

The database search was conducted on March 3rd, 2017, identifying 10,403 citations. Among these citations 1,971 duplicates were removed, leaving 8,432 citations. After the first level of screening, 124 citations proceeded to the full-text level of screening. A total of 22 remained after this level of screening. The following reasons for exclusion were as follows: the risk prediction model was not the primary intervention (n=43); the study was not conducted in primary care (n=11); the study assessed for outcomes not applicable to this study (n=13); the article only described the methods (n=6); the method of risk assessment did not incorporate a prediction model (n=16); the study only assessed for behavioural intentions, perceived risks, or knowledge (n=9); the model used measured a non-chronic outcome (n=1). The PRISMA flow chart depicting the screening process as per the PRISMA template is presented in Figure 2.[189]

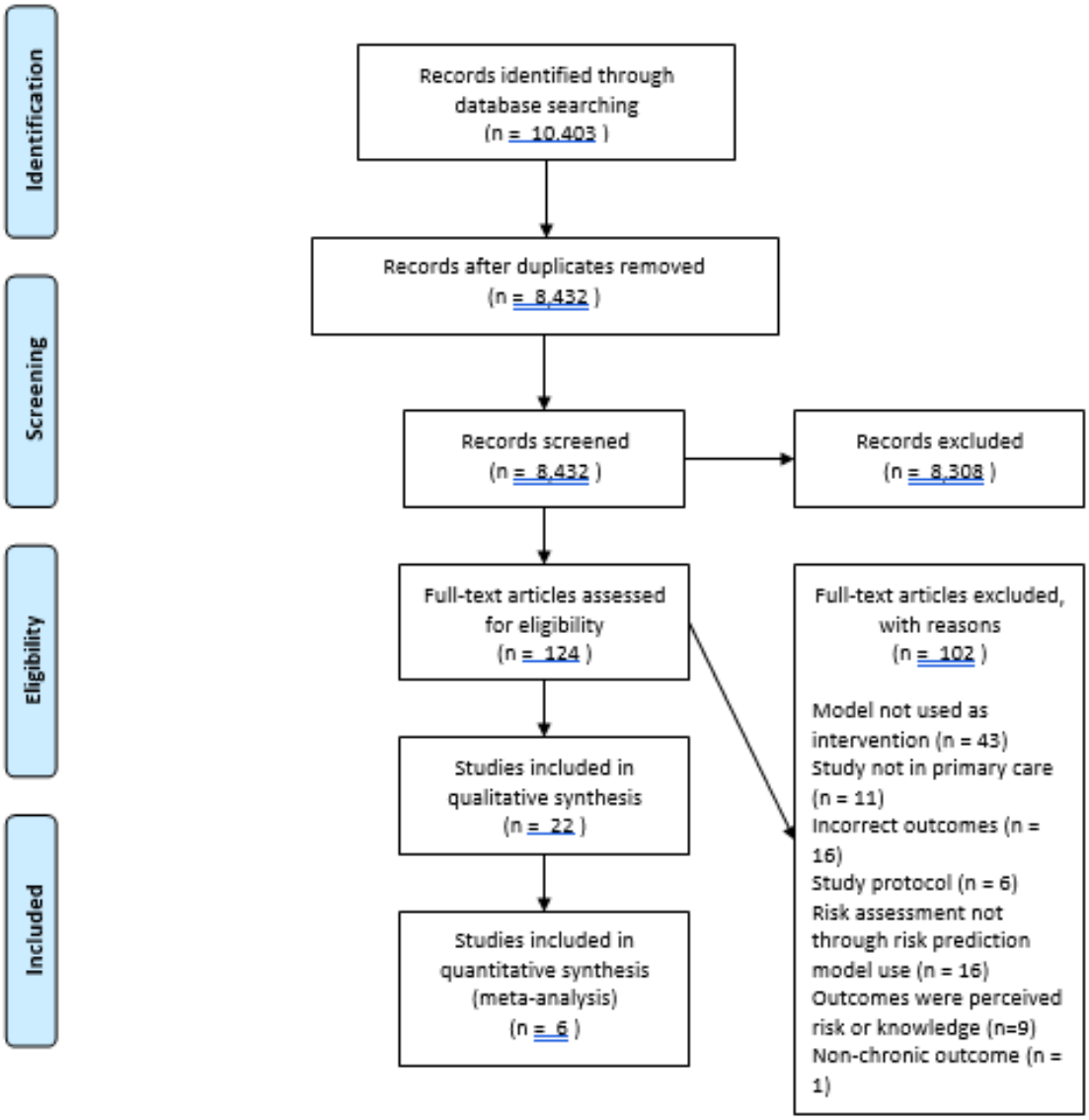

Figure 2. PRISMA flow chart.

5.2 Risk of bias assessment

The Downs and Black tool was used to assess the risk of bias for the included studies. Figure 11 displays the information using a bar graph. The risk of bias is presented as per the five domains assessed by the Downs and Black tool: 1) reporting, 2) external validity, 3) bias, 4) confounding, and 5) power. Cumulative scores are presented for each domain

pertaining to the level of bias present in the included studies. Overall, the score for risk of bias is 67.7%, indicating a moderate risk of bias.

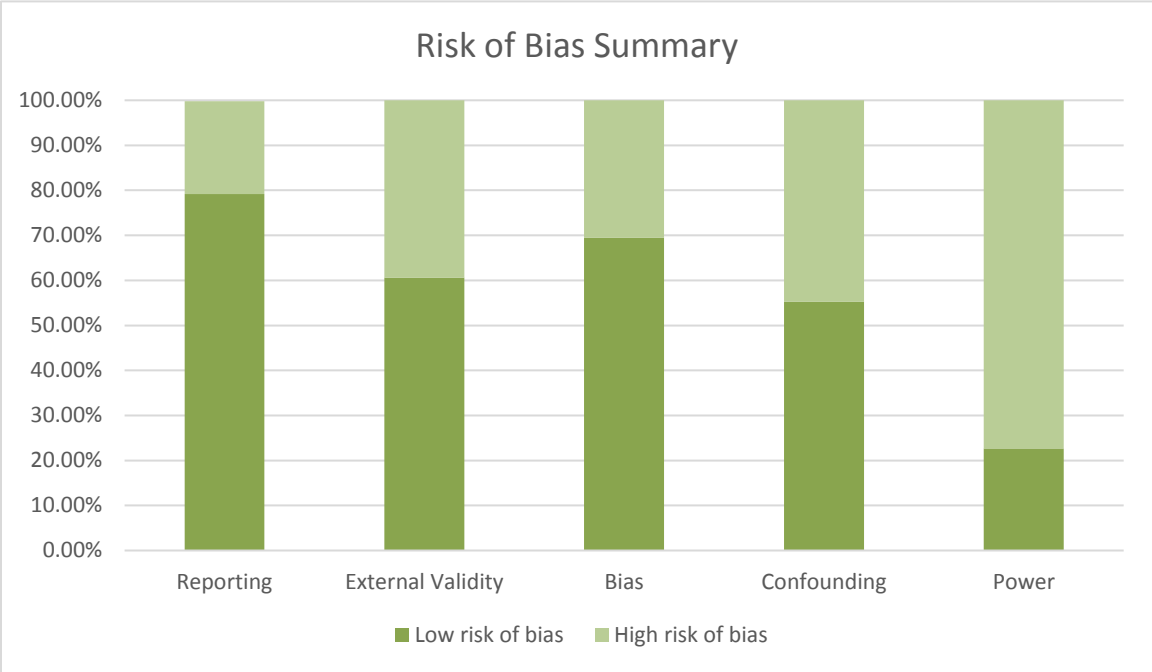

Figure 3. The risk of bias of the systematic review measured by compounding the risk of bias of individual studies.

5.3 Study characteristics

The study characteristics are presented according to demographic characteristics (Table 6) and intervention characteristics (Table 7).

5.3.1 Demographic characteristics

The studies were geographically diverse across developed nations, with representation from the United Kingdom (n=5), the United States (n=4), Canada (n=4), Denmark (n=3), the Netherlands (n=2), Australia (n=2), Hong Kong (n=2), Italy (n=2), and New Zealand (n=1). All the studies took place in a primary care setting under the supervision of one or more physicians, and reported on 400,758 patients. After accounting for loss to follow-up, a total of 383,005 patients remained. There was inconsistent reporting of number of physicians, with nine studies not providing a number of physicians, and five only providing the number of practices included. Six studies reported that there were 555

general practices. Of the 11 studies that reported a number of physicians, there were 3801 primary care physicians.

Most studies included patients who had a mean age over 50 years, with only 1 study including patients under the age of 18 years (Burgess et al., 2011). Distribution of patient sex varied greatly between studies. The full table of demographic characteristics is provided in Table 6.

Table 6. Demographic characteristics of studies included in the systematic review.

Author, country, year	Name of study	Patient inclusion	Number of participants (lost to follow-up)	% of male patients	Age of patients[a]
Bach-Nielsen et al., Denmark, 2005[199]	The Ebeltoft Project	- Receipt of elevated cardiovascular risk score	Patients: 14	64.3%	33-50 years
Bellows et al., USA, 2014[200]	IndiGO	- IndiGO total benefit score in top third	Patients: 489 Physicians: 10	66%	59
van den Brekel-Dijkstra et al., Netherlands, 2016[201]	Personalized Prevention in the Local Community (PPLC) Programme	- 45-70 years - No CVD or diabetes	Patients: 230 (101)	47.80%	52.2 (6.3)
Burgess et al., Australia, 2011[202]	AHC Study	- Residence in community for 3 years prior and post AHC participation - Elevated CVD risk - Participation in AHC program	Patients: 64 (6) Physicians: 15	67%	15-54
Chang et al., UK, 2016 UK[203]	NHS Health Check	- 40-74 years - Registered with practice participating in the Clinical Practice Research Datalink from April 1, 2009 to March 31, 2013 - No CVD or diabetes	Patients: 138,788 General practices: 462	Before matching: Attendees: 47.4% Nonattendees: 50% After matching: Attendees: 47.4% Nonattendees: 47.4%	Before matching: Attendees: 53.5 Non-attendees: 50.1 After matching: Attendees: 53.5 Non-attendees: 53.4
Cochrane et al., UK, 2012[204]	NHS Health Check	- Elevated CVD risk (≥20%)	Patients: Intervention: 365 (11)	Intervention: 90.1%	Intervention: 63.9 (6.5)

Author, country, year	Name of study	Patient inclusion	Number of participants (lost to follow-up)	% of male patients	Age of patients[a]
			Intervention plus: 236 (9) General practices: 38	Intervention plus: 86.4%	Intervention plus: 63.3 (6.4)
Courtney et al., US, 2015[205]	NA	- ≥30 years - No diabetes - Received PreDx test from June 2010 to December 2010	Patients: Intervention: 696 (139) Control: 2002 (1147)	Intervention: 60.1% Control: 60.0%	Intervention: 53 Control: 53
Engberg et al., Denmark, 2002[206]	NA	- 30-49 years by January 1, 1991	Patients: Intervention: 1006 (282) Control: 501 (132) Physicians: 9	Intervention: 48.8% Control: 48.3%	Intervention: 40.5 years (5.6) Control: 40.4 (5.8)
Ford et al., UK, 2001[207]	NA	- Patients who had a CHD risk request in 1998 at the Birmingham Heartlands Hospital	Patients: 906 General practices: 14	55.2%	NA
Grover et al., Canada, 2007[208]	The CHECK-UP Study	- 30-70 years	Patients: Intervention: 1510 (166) Control: 1543 (200) Physicians: 230	Intervention: 66.9% Control: 70.0%	Intervention: 56.4 (8.3) Control: 56.3 (7.9)
Grover et al., Canada, 2008[209]	The CHECK-UP Study	- 30-70 years	Patients: 2631 Physicians: 230	NA	Treatment initiation: Intervention: 56 (7.6) Control: 55.8 (7.9) Treatment modification: Intervention: 58.2 (7.6) Control: 58.3 (7.4)
Jiao et al., Hong Kong, 2014[210]	The RAMP-DM	- All persons with diabetes covered under general out-patient clinics in Hong Kong	Patients: Intervention: 1248 (176) Control: 1248 (176)	Intervention: 49.8% Control: 49.8%	Intervention: 64.3 (10.9) Control: 65.3 (11.7)
Jiao et al., Hong Kong, 2015[211]	The RAMP-DM	- ≥18 years - International Classification of Primary Care codes T89/T90 before participation	Patients: Intervention: 9094 Control: 9094	Intervention: 48.2% Control: 47.5%	Intervention: 64.23 (11.05) Control: 64.29 (11.96)

Author, country, year	Name of study	Patient inclusion	Number of participants (lost to follow-up)	% of male patients	Age of patients[a]
		- ≥ one public primary clinic visit before participation - No diabetes, cancer, chronic lung disease, and psychological conditions			
Law et al., Canada, 2014[212]	The PARADIGM Study	- Ambulatory men (≥40 years) and women (≥ 50 years) - No CVD or diabetes - No lipid-lowering medications at baseline	Patients: 3015 Physicians: 105	59%	56
Lowensteyn et al., Canada, 1998[213]	CHAS Study	- 30-74 years - No CVD	Patients: Intervention: 782 (580) Control: 176 (87) Physician: Intervention: 170 (73) Control: 83 (51)	Intervention: 64.8% Control: 64.8%	Intervention: 50.5 (10.8) Control: 50.7 (11.3)
Mehta et al., New Zealand, 2014[214]	PREDICT CVD-16	- 30-80 years - First risk assessment using PREDICT conducted between January 1, 2006, and October 15, 2009 - No CVD-related hospitalization - No anti-anginal medication dispensement	Patients: 90,631	56%	30-80
Palmieri et al., Italy, 2011[215]	CUORE Project	- 35-69 years - No CVD or prior cardiovascular event	Patients: 117,345 (12427) Physicians: 1032	44.7%	NA
Powers et al., USA, 2011[216]	NA	- ≥55 years - Enrolled in primary care for at least one year - ICD hypertension diagnosis with hypertensive medication prescription - Systolic blood pressure at least 140 mmHg or diastolic blood pressure at least 90 mmHg - Electrocardiogram within past five years	Patients: Intervention: 44 Control: 45 General practice: 1	98%	Intervention: 68 (9) Control: 65 (8)

Author, country, year	Name of study	Patient inclusion	Number of participants (lost to follow-up)	% of male patients	Age of patients[a]
		- No CVD, stroke, myocardial infarction, psychosis or dementia			
Price et al., UK, 2011[217]	Understanding Risk Study	- Increased CVD risk (≥20%) - Fluent in English (reading/writing) - No CVD or physical disability	Patients: Intervention: 99 Control: 95 9 patients lost to follow-up General practices: 4	67%	62.3
Romero et al., USA, 2008[218]	NA	- CHD risk more than 10% or diabetes with one other cardiac risk factor - Indication of prior CHD, bleeding risk, aspirin allergy, inadequate data, or low CHD risk	Patients: Pre-intervention: 294 Post-intervention: 202	Pre-intervention: 62% Post-intervention: 54.5%	Pre-intervention: 71 Post-intervention: 71
Usher-Smith et al., UK, 2015[219]	NHS Health Check	- Attend NHS Health Check between April 1, 2011 to December 1, 2014 - Risk between 10% to 20%	Patients: 410 (310)	56%	64.7 (6.11)
Sorensen et al., Denmark, 2011[220]	DanRisk Study (Danish Risk Score Study)	- Born in 1949 or 1959 - Live in Southern Denmark - No CVD or diabetes	Patients: 1156 (81)	Baseline: 47.1% Follow-up: 46.3%	Baseline: 50-year: 49.8% 60-year: 54.0% Follow-up: 50-year: 48.6% 60-year: 51.4%
Vagholkar et al., Australia, 2014[221]	NA	- 45-69 years - No CVD - Fluent in English - No cognitive impairments	Patients: Intervention: 567 (92) Control: 507 (76) General practices: Intervention: 20 (2) Control: 16	Intervention: 45% Control: 38.5%	Intervention: 56.2 (6.6) Control: 56.6 (6.9)
Volpe et al., Italy, 2007[222]	ForLife Study	- Diagnosed hypertension (both treated and untreated)	Patients: 12792 (1326) Treated: 7512 Untreated: 5280 Physicians: 1800	Treated: 51% Untreated: 49.6%	Treated: 68 Untreated: 64

Author, country, year	Name of study	Patient inclusion	Number of participants (lost to follow-up)	% of male patients	Age of patients[a]
Wind et al., Netherlands, 2015[223]	NA	- Type 2 diabetes mellitus treated with lifestyle advice and/or no more than two oral blood glucose lowering drugs	Patients: 933 (220) Physicians: 117	53.2%	64.4 (10.5)

[a] Age presented in years as: mean (standard deviation), and range, where applicable.

5.3.2 Intervention characteristics

Overwhelmingly, the risk prediction models used as the intervention or as a component of the intervention in each study predicted the risk of cardiovascular diseases. Twenty-one of the twenty-two studies included predicted for the long-term risk of either cardiovascular disease, coronary heart disease, myocardial infarction, or stroke. Of the 21 studies, 4 were predictive of cardiovascular disease amongst patients with diabetes. Only one of the twenty-two studies included predicted for type 2 diabetes. No studies examined risk prediction models that were predictive of either cancer or chronic respiratory diseases, two of the four WHO categorizations of chronic disease used in this systematic review.

The actual prediction models used varied; the majority (n=12) used a Framingham equation or derivative thereof. The next most common tool used was the UKPDS risk engine (n=3). Other tools used were SCORE (n=1), QRisk (n=2), the European HeartScore (n=1), PreDx (n=1), the JADE Classification System (n=2), the 10-CR Score (n=1), the Anggard Modified Risk Score (n=1) and the IndiGO Prediction Tool (n=1). One study did not specify which tool was used, and one other study used an unnamed multilevel linear regression equation as a component of the NHS UK Health Check.

Individual study designs were not always ascertainable because in some studies they were mixed. However, the general study methods employed by researchers were: randomized controlled trial (n=8), pre-post study (n=5), prospective cohort (n=5), retrospective cohort (n=4), case-control study (n=2), and qualitative interviews (n=1).

Fifteen of the twenty-five studies reported on physician behaviour. Patient behaviour was reported by 11 studies, and the patient health outcomes were reported by 17 studies. There is some overlap, with most studies reporting on multiple objectives. Complete intervention characteristics are presented in below (Table 7).

Table 7. Characteristics of the interventions presented in the included studies.

Author, year	Study design	Model	Outcome of model	Recruitment period	Follow-up	Study outcome(s)[b]
Bach-Nielsen et al., 2005[199]	Qualitative (interview)	Unknown	CVD risk	1991	4 years	- 2
Bellows et al., 2014[200]	Case-control (propensity score matched)	IndiGO Prediction Tool	5-year heart attack and stroke risk	November 2008-April 2009	3-6 months	- 1 - 3
van den Brekel-Dijkstra et al., 2016[201]	Pre-post	SCORE	10-year CVD risk	2012-2013	6 months	- 2
Burgess et al., 2011[202]	Pre-post	New Zealand Guidelines Group handheld chart (based on Framingham equations)	5- and 10-year CHD risk	March 2005-September 2005	3 years	- 1 - 2 - 3
Chang et al., 2016[203]	Retrospective cohort	QRISK2	10-year CVD risk	April 1, 2009-March 31, 2013	2 years (median)	- 1 - 2 - 3
Cochrane et al., 2012[204]	Randomized controlled trial	Multilevel linear regression equation	10-year CVD risk	September 2009-February 2010	12 months	- 3
Courtney et al., 2015[205]	Case-control study	PreDx	5-year risk of type 2 diabetes	June 2010-December 2010	Intervention: 17 weeks (mean) Control: 15 weeks (mean)	- 1 - 2 - 3
Engberg et al., 2002[206]	Randomized controlled trial (population-based)	Modified Anggard Risk Score	CVD	December 1991-June 1992	1 and 5 years	- 3
Ford et al., 2001[207]	Retrospective cohort (pre-post)	Framingham equations	10-year CHD risk	1998	NA	- 1
Grover et al., 2007[208]	Randomized controlled trial	Based on Framingham equations	10-year CVD risk	May 10, 2001-August 25, 2003	1 year (3 month intervals)	- 3

Author, year	Study design	Model	Outcome of model	Recruitment period	Follow-up	Study outcome(s)[b]
Grover et al., 2008[209]	Randomized controlled trial	Based on Framingham equations	10-year CVD risk	After August 2003	Baseline: 2-4 weeks following screening Follow-up visits: 3, 6, 9, and 12 months	- 1
Jiao et al., 2014[210]	Prospective cohort with matched exposure-non-exposure groups	JADE Classification System (Joint Asia Diabetes Evaluation Program) and 10-year Framingham Risk Function for CVD, and UKPDS for CHD and stroke	10-year CVD, CHD, and stroke risk	August 2009-June 2010	12 months	- 1 - 3
Jiao et al., 2015[211]	Prospective cohort	JADE Classification System (Joint Asia Diabetes Evaluation Program)	Diabetes microvascular complications (CHD, heart failure, stroke) and mortality	August 1, 2009-July 31, 2010	3 years (median)	- 1 - 2 - 3
Law et al., 2014[212]	Prospective cohort	Framingham risk score	CVD	March 2009-March 2010	NA	- 1
Lowensteyn et al., 1998[213]	Randomized controlled trial	8-year CHD prevention model (based on Framingham equations)	8-year CHD risk	NA	3-6 months	- 2 - 3
Mehta et al., 2014[214]	Prospective cohort	New Zealand adjusted risk score (based on Framingham risk score)	5-year CVD risk	January 1, 2006-October 15, 2009	Up to 3 years (6 month intervals)	- 1
Palmieri et al., 2011[215]	Pre-post (retrospective)	10-CR Score (from Progetto CUORE longitudinal studies)	10-year risk of fatal and non-fatal CVD events	January 2007-May 2010	Within 1 year of baseline	- 3
Powers et al., 2011[216]	Randomized controlled trial	Framingham Risk Score	10-year CHD and stroke risk	NA	3 months	- 2 - 3
Price et al., 2011[217]	Randomized controlled trial	UKPDS risk engine	10-year CVD risk	NA	1 month	- 1 - 2 - 3
Romero et al., 2008[218]	Retrospective cohort	Framingham risk score	10-year CHD risk	April 1, 2003-June 30, 2003	October 1, 2004-	- 1

Author, year	Study design	Model	Outcome of model	Recruitment period	Follow-up	Study outcome(s)[b]
					December 31, 2004 (18-21 months after baseline; 11-14 months after intervention)	
Usher-Smith et al., 2015[219]	Retrospective cohort	QRISK	10-year CVD risk	After December 1, 2014	28.0 (SD 10.3) months	- 2 - 3
Sorensen et al., 2011[220]	Pre-post	Europe HeartScore	10-year CVD mortality risk	2009	6 months	- 1 - 2
Vagholkar et al., 2014[221]	Cluster randomized controlled trial	New Zealand CV risk calculator (based on Framingham risk score)	CVD	2008-2010	12 months	- 1 - 3
Volpe et al., 2007[222]	Prospective cohort	Modified Framingham equations (modification to account for antihypertensive treatment)	10-year stroke risk	February 2003-July 2003	4±1.5 months	- 3
Wind et al., 2015[223]	Pre-post	UKPDS	10-year non-fatal and fatal CHD risk	NA	1.0±0.2 years	- 1 - 3

[b] 1=physician behaviour; 2=patient behaviour; 3=patient health outcomes.

5.3.3 Intervention descriptions

The studies each incorporated the use of a risk prediction model as a main component of their intervention. However, components in addition to the provision of absolute risk as derived by the risk prediction models were present in most of the studies such as providing measures of relative risk or threshold-dependent lifestyle advice. These characteristics could have their own impact on the study outcomes, providing a degree of heterogeneity between included studies. This section describes each study's application of risk prediction models and how the impact of the models was determined. A complete overview of each intervention is provided in Appendix D.

The presentation of risk to either the physicians or patients varied between studies. Modes of presenting risk also varied. Paper-based presentation of risk was the most

common, with 13 studies providing a printed risk profile. Second most common was a computer- or web-based presentation (n=8). In four of the studies, risk was communicated verbally between the physician and the patient. Some studies used multiple formats. For example, the risk may have been calculated using a computer-based software, and was subsequently printed for patients to take home (n=6). Lastly, in three studies it was not possible to determine how risk was presented.

In addition to the absolute measure of risk, some studies chose to provide a relative or additional representations of risk (n=9). Usher-Smith et al. provided patients with both the baseline QRisk score, as well as a projected score, demonstrating the effect of lifestyle changes. Bellows et al. provided the absolute risk of heart attack or stroke as well as projected absolute risks if interventions were implemented. Similarly, Price et al. provided the absolute risk as well as an achievable risk, an estimation of absolute risk if risk factor targets were met. Grover et al. 2007 and 2008 provided the absolute risk as well as a relative risk, comparing the patient to other Canadians matched for age and sex. Courtney et al. provided patients with their absolute likelihood of developing type 2 diabetes as well as compared to the general population. Lowensteyn et al. presented the 8-year coronary risk as well as how much the risk would be reduced if one or more risk factors were modified. Palmieri et al. provided two additional measures of risk: first, a hypothetical risk for a person of the same age and sex as the patient with favourable modifiable risk factor levels, and secondly, the risk of a smoker one year after smoking cessation and with a decrease of 10% in modifiable risk factors. Alongside their personal risk, Powers et al. also presented the average and optimal risk for the patient's 5-year age group in graphical format.

Eleven studies chose to incorporate lifestyle advice in addition to the provision of the patient's absolute risk. Cochrane et al. included consultation with lifestyle coaches who assisted in developing health improvement plans, in addition to setting priorities for lifestyle goals. Usher-Smith et al. provided all participants with an information leaflet including recommendations for individuals to improve their lifestyle through smoking cessation, healthy diet, reduction in alcohol consumption, and physical activity. Bach Nielsen et al. provided feedback, including lifestyle modification advice, to their patients

when their calculated risk and risk factor values fell outside of normal range. van den Brekel-Dijkstra et al. personalized the lifestyle advice to each patient based on their risk profile, the associated risks and benefits of preventive action, and individual opportunities for lifestyle change depending on motivation, self-efficacy, and preferences. Chang et al. 2016 evaluated the NHS Health Check, which provides a risk assessment allowing for a tailored strategy for patient management, including lifestyle advice. Engberg et al. provided 45-minute consultations with a general practitioner where lifestyle-related goals were established for the following year as well as providing all patients with a pamphlet on leading health lifestyles as per the Danish Heart Foundation. Palmieri et al. provided patients with lifestyle recommendations pertaining to nutrition, physical activity, and smoking cessation. Strategies to improve risk through risk factor modification (e.g. medication, patient lifestyle factors) were presented to intervention patients by Powers et al. Price et al. chose a more interactive format for patients to receive lifestyle advice, with a self-conducted slide show aimed at first setting goals to reduce risk, and the direction of behaviours towards achievement of goals. The intervention used by Bellows et al. included a face-to-face discussion of options for risk reduction providing a more tailored approach. Upon inclusion in the study, Burgess et al. provided a patient-centered consultation to discuss chronic disease care planning, which includes patient education and goal setting, in addition to consultations at each point of follow-up with either a remote access nurse or an Aboriginal health worker.

Decision support was a component of three studies, providing physicians with recommendations regarding patient management given a specific threshold of risk (i.e. targeting high risk patients). The JADE classification system stratifies patients as low, medium, or high risk; decision support was provided in terms of recommending appropriate interventions and education based on the risk threshold. Romero et al. provided decision support in the form of a poster providing a visual representation of the guideline recommended thresholds for aspirin initiation to prevent CHD.

Four studies incorporated referrals to other health care professionals as a component of the intervention. van den Brekel-Dijkstra et al. provided links to local providers of lifestyle interventions with suggestions for individual activities, group activities, or online

services, allowing for a variety of evidence-based lifestyle programs to be pursued by participants. The RAMP-DM intervention provided referrals to a team of healthcare professionals, including registered nurses, advanced practice nurses, optometrists, dietitians, podiatrists, physiotherapists amongst others dependent upon the patient's stratified risk level. Cochrane et al. provided referrals to free support sessions regarding weight management, physical activity, dietary counselling, and positive thinking upon request by participants.

Lastly, only three studies specifically reported that training was provided to physicians regarding the implementation of the intervention. Physicians in the Vagholkar et al. study were provided a 3-hour workshop regarding the use of the risk calculator, as well as the corresponding guideline-based recommendations for the risk strata. Physicians in the Palmieri et al. study incorporated training as per a national program regarding the assessment of cardiovascular risk using the 10-CR score, methods for identifying patients eligible for counseling or treatment, promoting shared decision-making, and evaluating and discussing collected data. Study sponsors in the Wind et al. study instructed physicians on how to use the UKPDS risk engine, interpretation of CHD risk, and appropriate prescription of medication.

5.4 Outcome descriptions

Presented in this section is an overview of the outcomes of each included study as they correspond to the three objectives of this systematic review. First is a summary of studies that assessed for changes in physician behaviour (n=15), then an overview of study outcomes pertaining to patient behaviour (n=11), and lastly a summary of changes in patient health outcomes (n=17).

5.4.1 Physician behaviour

Eleven studies assessed for the impact of risk prediction model use on physician behaviour. Each of these studies chose to measure the impact of prediction model use specifically on prescribing patterns. Differences or changes in prescription pattern were measured for several types of drugs, but primarily in five categories: lipid-lowering

medications (n=10), antihypertensives (n=9), antidiabetics including insulin and glucose-lowering medications (n=5), aspirin (n=3), and antiplatelets (n=2). Of these 11 studies, 9 found a statistically significant improvement in prescription with at least one of the risk reducing medications. One study also measured the monitoring of risk factors between the intervention and control group.

Sorensen et al. examined the change in prescription of antiplatelets, antihypertensives, and lipid-lowering medications from baseline to the six month follow-up.[220] Amongst patients with low risk (n=842), defined as <5% 10-year cardiovascular mortality risk, prescription with antiplatelets increased from 18 patients at baseline to 19 at follow-up (p=0.71), prescription with lipid-lowering medication increased from 84 to 94 patients (p=0.07), and prescription with antihypertensives increased from 151 to 163 patients (p=0.04). Amongst patients with high risk (n=233), defined as ≥5% 10-year cardiovascular mortality risk, prescription with antiplatelets increased from 14 to 17 patients (p=0.32), prescription with lipid-lowering medication increased from 25 to 44 patients (p<0.0001), and prescription with antihypertensives increased from 55 to 74 patients (p=0.0009). Overall (n=1075), prescription with antiplatelets increased from 32 to 36 patients (p=0.32), lipid-lowering medication from 109 to 138 (p<0.0001), and antihypertensives from 206 to 237 (p=0.0002).

Chang et al. compared the prescription for statins or antihypertensive medication between the intervention group (n=29,672) and the control group (n=109,116). The crude numbers of prescription with antihypertensives and statins is presented in Appendix E. After propensity score matching, the intervention was associated with significantly greater increases in percentage of participants being given a statin (3.83%, 95% CI 3.52, 4.14) and antihypertensive prescription (1.37%, 95% CI 1.08, 1.66).

Vagholkar et al. assessed for changes in antihypertensive and lipid-lowering medications at baseline and a 12-month follow-up in both the intervention and control group, as well as treatment intensification or reduction. Amongst intervention patients (n=475), antihypertensive prescription increased from 136 (28.6%) to 148 patients (31.2%), with 56 patients (11.8%) having their prescription intensified and 32 (6.7%) having reductions.

Lipid lowering increased from 101 (21.3%) to 108 (22.7%), with 37 (7.8%) intensified and 24 (5.1) reduced. 59 patients (12.4%) were prescribed both at baseline and 63 (13.3%) at follow-up. Amongst control patients (n=431), antihypertensives increased from 133 (30.9%) to 148 (34.3%) at follow-up, with 46 (10.7%) having their prescription intensified and 25 (5.8%) having it reduced. For lipid-lowering medications, 120 (27.8%) were prescribed at baseline and 130 (30.2%) at follow-up, with 41 experience intensifications (9.5%) and 26 experiencing reductions (6.0%). 60 control patients (13.9%) were prescribed both at baseline, and 69 (16.0%) at follow-up. Changes in pharmacologic management were not statistically significant except for the increase in patients on antihypertensives within the control group (30.9% to 34.3%, p=0.03).

Grover et al. (2008) assessed for the initiation and intensification of antihypertensive medication between the risk profile group (n=629) and the control group (n=668). 34.9% of risk profile patients increased treatment compared to 27.7% of control patients, with a difference of 7.2% (95% CI 1.1, 13.3; $p<0.05$). For treatment initiation, 31.4% of risk profile patients started antihypertensives compared to 24.1% of control patients, with a difference of 7.3% (95% CI -1.4, 15.9). Overall, 33.8% of risk profile patients initiated or increased treatment compared to 26.7% of control patients with a difference of 7.1% (95% CI 2.1, 12.1; $p<0.01$).

Courtney et al. found that there were higher rates of prescription amongst risk-tested patients for all medications examined (antihypertensives, lipid-lowering, antidiabetics, and aspirin) during the follow-up period compared to the control group; no numeric figures were provided. They also found that patients who received the risk test were more likely to receive follow-up measurements of risk factors compared to control patients, including blood pressure (91.5% versus 42.7%), weight (91.1% versus 42.8%), LDL-cholesterol (71.8% versus 24%), HDL-cholesterol (72.7% versus 24.3%), HbA1c (58.6% versus 11.5%), triglycerides (96.8% versus 82.8%) and fasting glucose (98.4% versus 72.4%). All differences reached statistical significance ($p<0.001$), and indicate more careful and targeted monitoring for risk-tested patients compared to control patients.

In a pre-post study design, Ford et al. found that at baseline, 10.7% of patients (97/906) were prescribed with statins, and 11% (100/906) after coronary heart disease risk assessment. Amongst those with a 10-year CHD risk of <30% (n=825), 62 patients were already taking a statin, 4 patients discontinued statin use, and 4 patients began statin use. Amongst patients with a 10-year CHD risk of 30% or greater (n=81), 35 patients were already taking a statin, and 3 patients began a statin.

Jiao et al. (2015) assessed the prescription of 4 medications (glucose-lowering, antihypertensive, and lipid-lowering drugs, and insulin) at baseline and following the implementation of the RAMP-DM intervention for both the risk profile group (n=9094 baseline; n=8892 follow-up) and the control group (n=9094 baseline; n=8542 follow-up). At baseline, 87.3% of intervention patients were prescribed glucose-lowering drugs at baseline compared to 87.2% of control patients ($p=0.755$); at follow-up, 90.0% of intervention patients were compared to 83.6% of control patients ($p<0.001$). For antihypertensive drugs, 73.0% of intervention patients were prescribed compared to 73.4% of control patients at baseline ($p=0.547$), while at follow-up, 80.0% of intervention patients were prescribed compared to 76.0% of control patients ($p<0.001$). 13.1% of intervention patients were prescribed lipid-lowering drugs at baseline compared to 13.5% of control patients ($p=0.431$), while at follow-up 51.2% of intervention patients were prescribed compared to 45.7% of control patients ($p<0.001$). Lastly, 1.2% of intervention patients were prescribed insulin at baseline compared to 1.4% of control patients ($p=0.101$) and at follow-up, 6.0% of intervention patients were prescribed insulin compared to 4.5% of control patients ($p<0.001$).

Jiao et al. (2014) assessed the RAMP-DM intervention and its impact of prescription with glucose-lowering drugs, insulin, antihypertensive drugs, and lipid-lowering drugs as well from baseline to a 12-month follow-up within the intervention and control arm. Only differences in insulin prescription were significant at both baseline and follow-up (baseline: $p<0.001$; follow-up: $p<0.001$). Differences in prescription at baseline and follow-up for glucose-lowering medications (baseline: $p=0.593$; follow-up: $p=0.207$), antihypertensive drugs (baseline: $p=0.382$; follow-up: 0.302), and lipid-lowering drugs (baseline: $p=0.437$; follow-up: $p=0.354$) were not statistically significant.

Price et al. made note of risk-reduction prescriptions from baseline to follow-up amongst intervention and control groups, and found a greater number of prescriptions were given to those for whom risk was calculated. Amongst the intervention patients, there were 17 new prescriptions in 12 individuals compared to 5 new prescriptions in 5 individuals in the control group ($p=0.01$). Specifically, in the intervention group, there were new prescriptions for aspirin (n=2), antihypertensives (n=8), glucose-lowering medications (n=3), and lipid-lowering medications (n=4).

Romero et al. assessed for changes in aspirin prescription in a retrospective analysis. They found that at baseline, 63.5% (127/202) patients used aspirin for the primary prevention of CHD, while the post-intervention rate of aspirin use was 72.8% (147/202), representing a 9.3% ($p=0.054$) absolute increase in rate of aspirin use, indicating a marginally insignificant result.

Bellows et al. reported on the impact of the IndiGO individualized clinical guidelines on new prescription of statins and antihypertensives. Though no difference was found between intervention (n=489) and control (n=489) groups with regards to antihypertensive medication (17% versus 15%, $p=0.39$), patients in the intervention group were significantly more likely to be prescribed statins compared to control patients (39% versus 8%; $p<0.01$).

Burgess et al. examined the impact of the Aboriginal and Torres Strait Islander Adult Health Check on prescription of medications related to CVD risk reduction in a pre-post study design. At baseline (n=64), 18 patients (28%) were prescribed, and at follow-up (n=63), 56 patients (89%) were prescribed. Significant increases in prescription from baseline to follow-up were found for antiplatelets (4.7% to 68.3%, $p<0.001$), lipid lowering medication (6.3% to 65.1%, $p<0.001$), angiotensin converting enzyme inhibitors/angiotensin receptor blockers (25% to 63.5%, $p<0.001$), and oral hypoglycemic medications (17.2% to 33.3%, $p=0.04$) were found. No significant increase in prescription with beta blockers (4.7% to 12.7%, $p=0.09$), nitrates (3.1% to 4.8%, $p=0.49$), thiazide diuretics (0% to 3.2%, $p=0.24$), or calcium channel blockers (1.6% to 1.6%, $p=0.75$) were found.

5.4.2 Patient behaviour

Risk reducing patient behaviours as a result risk prediction models use were examined in 11 studies. A greater number of measures were studied when compared to practitioner behaviours. Most common was cigarette smoking, with eight studies evaluating the impact of risk prediction models use on smoking cessation. Other measures evaluated included changes in physical activity (n=4), diet (n=2), medication use (n=2), continuity of care or return for follow-up visit (n=2), and alcohol consumption (n=1). Of the eight studies examining smoking cessation, two studies found a significant result, while six were non-significant. Of the six studies, three studies demonstrated a non-significant absolute reduction of smoking prevalence, while one study reported a significant reduction in number of cigarettes smoked per day. Though all the studies reporting changes in physical activity noted increases in exercise levels, none reported a significant change; two stated there was a non-significant effect, one was conducted qualitatively, and one only reported the change in proportions.

van den Brekel-Dijkstra et al. examined patient behaviour through use of a pre-post study design. Of the patients that responded to the follow-up questionnaire (56%), 40 of 129 (31%) patients reported initiations of health behaviour change, 41 (32%) reported improvements in physical activity, and 36 (28%) improved their diet. 23 of 96 (24%) current drinks reduced their alcohol intake. Forty four percent (6/16) current smokers reduced or quit smoking.

Usher-Smith et al. conducted a study examining the change of statin prescription threshold from 20% absolute cardiovascular risk to 10%, the corresponding provision of a cardiovascular risk score to the patient, and subsequently the patients' decision regarding statin prescription. In this fashion, the onus of statin prescription fell unto the patients. Among 410 statin-naïve patients, 45 (11%) chose to start a statin. An association was found between increasing QRisk score and statin initiation (OR 1.34 (1.13, 1.60)).

Sorensen et al. examined smoking cessation amongst participants. At baseline, 253 of 1075 (24%) participants were current smokers. At follow-up, 39 participants had quit

smoking, while 10 subjects started smoking again. The number of active smokers decreased to 224 ($p<0.0001$). Similarly, Wind et al. found that among their participants in a pre-post study design (n=713), the percentage of smokers decreased from 18.3% at baseline to 15.0% at follow-up ($p<0.05$).

Chang et al. also examined smoking cessation between the intervention and the control group. Complete smoking prevalence is presented in Appendix E. Smoking prevalence decreased more in the intervention group than in the control group; after propensity score matching, the difference in prevalence was -0.11% (95% CI -0.35, 0.13), though not statistically significant.

Jiao et al. (2015) assessed patients for smoking status at both baseline and follow-up in the intervention and control groups, and found no significant change in smoking status at the end of follow-up between groups (smoking prevalence of 10.2% and 10.0% at baseline for the intervention and control groups, respectively, $p=0.605$; smoking prevalence of 9.0% and 8.6% at follow-up for intervention and control groups, respectively, $p=0.651$), though both groups did experience a reduction in smoking prevalence.

Lowensteyn et al. noted the absolute change in number of smokers among those who were reassessed between intervention (n=202) and control groups (n=89). 20.8% of intervention groups were smokers at baseline; at follow-up, 3 had quit smoking for an absolute change of -1.5%. Comparatively, in the control group, at baseline there were 21 smokers (23.6%); at follow-up, 2 people had quit smoking (absolute change: -2.3%). The difference in absolute change between intervention and control groups was 0.8% ($p=0.64$). Though a greater absolute change was noted in the control group, it was statistically non-significant.

Though the Australian Health Check found a decrease in percentage of smokers from 83% at baseline to 78% at follow-up, the decrease was not significant ($p=0.51$). However, the number of cigarettes smoked per day did decrease significantly ($p<0.001$), from 3.5 (SD 0.1) to 2.6 (SD 0.2) according to smoking categories.

Bach Nielsen et al. conducted a qualitative study examining the effect of cardiovascular risk scores on lifestyle changes. Several participants made radical changes, contacting dietitians and reorganizing their diets, involving their families and cooking different types of food for different family members, and began exercising. These changes were only to the extent that their perceived quality of life wouldn't suffer, what the authors referred to as the "pain limit". Others took an active interest in their progress over time, asking their general physician for examinations to determine whether their efforts had any effect.

Courtney et al. reported that patients assessed for risk of diabetes (n=696) as determined by the PreDx risk score were more likely to return for a follow-up visit than the control group (n=2002). 80% of the risk group (557/696 patients) returned for a visit compared to the control group, where 42.7% (800/2002) returned, indicating the intervention positively influenced the likelihood of continuity of care.

Powers et al. reported on three aspects of patient behaviour: self-reported medication adherence, current exercise level, and smoking. They then compared the intervention and control arms for between-group differences. For self-reported medication adherence, at baseline, 50% of the intervention arm reported medication adherence compared to 51% of the control patients; at 3 months, 46% in the intervention arm compared to 49% in the control arm reported medication adherence (p=0.55). Patients in both arms improved the amount of exercise they engaged in (48% to 57% from baseline to follow-up in intervention arm, 42% to 53% from baseline to follow-up in the control arm, p=0.77). Smoking cessation occurred in the intervention group, decreasing from 18% to 14%, while it remained at 18% at both baseline and follow-up in the control arm (p=1.00). Overall, no significant differences were noted when comparing self-reported medication adherence, current exercise levels, and smoking status between intervention and control arms.

Price et al. monitored physical activities in all participants using a hip-worn accelerometer measuring the amount and intensity of human activity. Though 53% of participants increased their physical activity, there was a non-significant net 0.5% (95% CI -0.6, 1.8) increase in accelerometer counts in the intervention group (p=0.56).

5.4.3 Patient health outcomes

Fourteen studies explored the impact of prediction models on patient health outcomes. Commonly assessed were the impact on biometric, or risk factor, values (n=13) as well as on estimated absolute risk of health outcome (n=13). Specific risk factor values evaluated were: systolic blood pressure (n=10), diastolic blood pressure (n=8), HDL cholesterol (n=8), total cholesterol (n=7), BMI (n=7), LDL cholesterol (n=6), total cholesterol to HDL cholesterol ratio (n=4), HbA1c levels (n=4), weight (n=2), and two studies examined blood pressure without specification of diastolic or systolic. Only three studies examined event rates, specifically cardiovascular disease (n=2), coronary heart disease (n=2), stroke (n=1), heart failure (n=1), all-cause mortality (n=1), and type 2 diabetes mellitus (n=1).

Chang et al. compared to the absolute reduction in cardiovascular risk between the intervention group and control group, finding the intervention group (n=29,672) reduced their 10-year cardiovascular risk from 6.7% (SD 5.9) to 6.2% (SD 5.3) with a difference of -0.48% (95% CI -0.5, -0.46), while the control group (n=109,116) reduced their risk from 5.1% (SD 5.3) to 4.9% (SD 5.0), with a difference of -0.19% (95% CI -0.19, -0.18). The crude differences-in-differences between the intervention and control group was -0.29% (95% CI -0.31, -0.27), and after propensity-score matching, was -0.21 (95% CI -0.24, -0.19).

Chang et al. also reported on changes in risk factors, namely systolic blood pressure, diastolic blood pressure, body mass index, and total cholesterol. The crude levels of risk factors are provided in Appendix E. After propensity score matching, the following reductions in risk factor values comparing the intervention group to the control group were found to be significant: systolic blood pressure (-2.51 mm Hg, 95% CI -2.77, -2.25), diastolic blood pressure (-1.46, 95% CI -1.62, -1.29), BMI (-0.27, 95% CI -0.34, -0.20), and total cholesterol (-0.15 mmol/L, 95% CI -0.18, -0.13).

Cochrane et al. had two groups: the NHS Health Check group and the NHS Health Check plus additional support group. Baseline and 1-year follow-up measures were collected for both trial arms. Both groups showed similar beneficial reductions in risk factors:

about 7 mmHg in systolic blood pressure, 4 mmHg in diastolic blood pressure, 0.65 mmol/L in total cholesterol, 0.5 in total cholesterol/HDL ratio, and 2 cm in waist circumference. Changes in HDL cholesterol, weight, and BMI were negligible, though a small significant reduction in overall BMI was noted (0.3 kg/m^2). Complete figures are available in Appendix F.

Cochrane et al. also noted changes in absolute CVD risk from baseline to 1-year follow-up (Appendix F). In the Health Check group, absolute risk was reduced from a mean of 32.9% (SD 9.7) at baseline (n=365) to 29.4% (SD 9.7) at follow-up (n=295). In the Health Check plus group, absolute risk was reduced from 31.9% on average amongst 236 participants to 29.2% (SD 10.1) at follow-up (n=191). This difference corresponds to a relative risk of 0.89 (95% CI 0.87, 0.92) amongst the Health Check group, and a relative risk of 0.91 (95% CI 0.88, 0.94) amongst the Health Check plus group.

Courtney et al. found that significantly more risk-tested patients experienced improvements in risk factor levels, including weight, blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, and HbA1c levels (all differences were statistically significant at $p<0.001$). The total percentages of patients with improved risk factors was not provided.

Grover et al. (2007) conducted a randomized controlled trial comparing patients receiving a risk profile (n=1510 baseline; n= 1344 follow-up) to usual care patients (n=1543 baseline; n=1343 follow-up). Changes in risk factor levels from baseline to the 12-month follow-up were reported, as well as the difference in changes between intervention and control patients. Intervention patients showed absolute changes of -58.4 mg/dL (SD 34.1) for total cholesterol, -51.2 mg/dL (SD 29.5) LDL cholesterol, 1.0 mg/dL (SD 6.0) HDL cholesterol, -1.5 TC:HDL cholesterol ratio (SD 1.1), -6.3 mmHg (SD 13.5) systolic blood pressure, and -3.8 mmHg (SD 7.9) diastolic blood pressure. Control patients showed absolute changes of: -54.5 mg/dL (SD 35.4) total cholesterol, -48.0 mg/dL (SD 29.7) LDL cholesterol, 0.8 mg/dL (SD 5.7) HDL cholesterol, -1.3 (SD 1.0) TC:HDL cholesterol ratio, -5.3 mmHg (SD 13.2) systolic blood pressure, and -3.6 mmHg (SD 7.7) diastolic blood pressure. Difference between the intervention and usual care group were:

-3.9 (p=0.02) total cholesterol, -3.3 (p=0.02) LDL cholesterol, 0.2 (p=0.37) HDL cholesterol, -0.1 (p=0.002) TC:HDL ratio, -0.9 (p=0.005) systolic blood pressure, and -0.2 (p=0.01) diastolic blood pressure.

Grover et al. (2007) also assessed the likelihood of high risk patients in either the intervention or control group reaching lipid target levels. Intervention patients were more likely to reach their lipid targets (OR 1.26; 95% CI 1.04, 1.53). They found that 70% of intervention patients were identified as high risk, and 57% reached their lipid targets, while 68% of control patients were identified as high risk, and 54% reached their lipid targets. When patients of all risk levels were considered, the intervention group was no more likely to reach their target lipid levels than the control group (55.2% versus 52.2%; OR 1.13, 95% CI 0.98, 1.30). For changes in 10-year cardiovascular disease risk, intervention patients experienced an absolute change of -5.9% (SD 4.5) while control patients experienced an absolute change of -5.3% (SD 4.3), with a difference between the two groups of -0.6% ($p<0.001$), indicating that intervention patients obtained a statistically significant reduction in absolute risk when compared to control patients.

Jiao et al. (2015) assessed for changes in risk factor levels from baseline to the 3-year follow-up point between intervention and control groups, including BMI, systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol, both HDL and LDL cholesterol, triglyceride levels, and estimated glomerular filtration rates. Though baseline characteristics with comparable between both arms, the intervention group experienced significant changes ($p<0.001$) for both systolic and diastolic pressure, HbA1c levels, total cholesterol, and both HDL and LDL cholesterol levels. Further, a greater percentage of intervention patients achieved treatment targets for blood pressure and HbA1c levels compared to control patients ($p<0.001$). Complete figures are available in Appendix G.

Jiao et al. (2015) also reported the rates of cardiovascular disease, coronary heart disease, stroke, heart failure, and all-cause mortality at 36 months in both study arms. 4.39% of intervention patients developed CVD compared to 6.69% of control patients; 1.87% experienced CHD compared to 3.08% of control patients; 2.25% of intervention patients

experienced a stroke compared to 3.40% of control patients; 0.79% of intervention patients experienced heart failure compared to 1.37% of control patients; and lastly, all-cause mortality incidence was 2.22% in the intervention group compared to 6.07% in the control group. Jiao et al. (2015) also constructed a multivariable Cox proportion hazard regression model comparing the intervention to the control group, adjusting for sociodemographic and clinical characteristics. The following hazard ratios were calculated: CVD (0.629, 95% CI 0.554, 0.715, $p<0.001$), CHD (0.570, 95% CI 0.470, 0.691, $P<0.001$), stroke (0.652, 95% CI 0.546, 0.780, $p<0.001$), heart failure (0.598, 95% CI 0.446, 0.802, $p=0.001$), and all-cause mortality (0.363, 95% CI 0.308, 0.428, $p<0.001$).

Jiao et al. (2014) examined the effect of the RAMP-DM from baseline to follow-up in the intervention arm of their study compared to the control arm for changes in biomedical outcomes, predicted cardiovascular risk, and percent of participants reaching treatment targets. In a fully adjusted model, differences between groups for changes in HbA1c levels ($p<0.05$), diastolic blood pressure ($p<0.05$), reaching treatment targets for diastolic blood pressure ($p<0.05$), the UKPDS 10-year CHD risk ($p<0.05$), the UKPDS 10-year stroke risk ($p<0.01$) were found to be significant, with intervention patients experiencing greater improvements. Cardiovascular events found to be significant were observed CHD ($p<0.001$) and total CVD ($p=0.003$), with RAMP-DM patients experiencing significantly fewer events.

Lowensteyn et al. reported the absolute changes in risk factors and 8-year coronary risk from baseline to follow-up in both the intervention arm (n=202) and the control group (n=89) amongst patients who were reassessed. Statistical significance was found for 8-year coronary risk (difference in absolute change between intervention and control group: -1.426%, $p<0.01$). Intervention patients compared to control patients also experienced a greater absolute change for total cholesterol (-0.49 mmol/L (SD 0.99) versus -0.09 (SD 0.87); estimated group difference -0.238, $p<0.05$), LDL-cholesterol (-0.40 (SD 0.87) versus -0.01 (SD 0.80); estimated group difference -0.226, $p<0.05$), and the total-cholesterol/HDL-cholesterol ratio (-0.6 (SD 1.3) versus -0.2 (SD 1.2); estimated group

difference -0.287, $p<0.05$). Non-significant changes were found for HDL-cholesterol, systolic and diastolic blood pressure, and BMI.

Palmieri et al. obtained complete data on 5,948 patients (3185 men, 2763 women). Amongst the men, 305 (10%) improved their risk factors, shifting from the high- or moderate-risk category to the low-risk category. 162 women (6%) shifted from high or moderate risk to low risk. Overall numbers for all participants was not reported.

Powers et al. reported on changes in systolic and diastolic blood pressure, and changes in 10-year CHD and stroke risk from baseline to follow-up amongst intervention and control groups. The between-group differences were not significant for any of the changes, indicating that the intervention did not have an effect in this study. The risk estimate for CHD was found to have increased at follow-up for both the intervention (25.0% (SD 1.6) to 26.9% (SD 1.8)) and control (24.1% (SD 1.5) to 24.6% (SD 1.8)) as well as the risk estimate for stroke (intervention: 21.0% (SD 2.3) to 23.3% (SD 2.7); control: 17.9% (SD 2.3) to 18.0% (SD 2.6)). Further, diastolic blood pressure was found to have increased at follow-up for both groups (intervention: 73.5 mmHg (SD 1.9) to 74.9 mmHg (SD 2.0); control: 76.6 mmHg (SD 1.8) to 76.7 mmHg (SD 1.9)). Only systolic blood pressure decreased in both arms (intervention: 128.4 mmHg (SD 2.7) to 128.2 mmHg (SD 2.9); control: 126.0 mmHg (SD 2.7) to 125.0 mmHg (SD 2.8)).

Price et al. also reported on changes in risk factor levels from baseline to follow-up in the intervention and control arms. Non-significant within or between group differences were found for weight, blood pressure, HDL cholesterol, triglyceride levels, or estimated 10-year CVD risk (no values were provided). However, a net 7% (95% CI -11.7, -3.2, $p=0.004$) decrease in mean LDL-cholesterol was found in the intervention arm.

Volpe et al. sought to determine the impact of a systematic stroke risk assessment on patients with hypertension that are treated (n=6971) and untreated (n=4718). They reported a significant decrease is both systolic and diastolic blood pressure from baseline to follow-up in both the treated and untreated patients. The treated group presented with baseline blood pressure (systolic/diastolic) of 150.1/87.4 mmHg and a follow-up of 136.7/81.0 mmHg, while untreated groups presented with a baseline blood pressure of

158.9/93.2 mmHg and a follow-up of 135.6/81.5 mmHg, with both differences highly significant ($p<0.0001$). Amongst all patients, there was a significant reduction of 13.3% in absolute stroke risk score, which the researchers attributed to the reduction in blood pressure.

Wind et al. examined the effect of the UKPDS risk engine on clinical management of coronary heart disease in a pre-post study design. At baseline, patients (n=713) had a 10-year CHD risk of 18.7% (SD 11.7); at follow-up, the absolute risk increased to 20.1% (SD 13.7). The increase in absolute risk was significant ($p<0.05$). Significant decreases ($p<0.05$) were also noted from baseline to follow-up for systolic blood pressure (139.8 mmHg (SD 17.7) to 138.3 mmHg (SD 16.4)), total cholesterol (4.5 mmol/L (SD 1.0) to 4.4 mmol/L (SD 1.0)), and BMI (31.1 (SD 5.2) to 30.8 (SD 5.3)). Nonsignificant changes in HbA1C (6.7% (SD 0.8) to 6.6% (SD 0.9)) and HDL cholesterol (1.2 mmol/L (SD 0.3) to 1.2 mmol/L (SD 0.3)) were reported as well.

The IndiGO clinical guidelines as assessed by Bellows et al. was assessed for its impact on predicted 5-year risk of heart attack or stroke. The intervention group experienced a reduction in risk from 6.7% at baseline to 5.1% at follow-up, a significant reduction compared to the control group, which experienced a reduction from 7.5% to 6.5% ($p=0.015$). Non-significant reductions in LDL cholesterol and systolic blood pressure were also noted, with LDL reductions of 114 to 106 in the intervention group and 114 to 109 in the control group ($p=0.37$), and systolic blood pressure reductions from 134 to 125 in the intervention group and 137 to 131 in the control group ($p=0.07$). No units were provided for blood pressure or LDL cholesterol levels. Though numeric values were not provided, there were no significant between-group differences in BMI change.

Burgess et al. examined the impact of prediction models on risk factors for CVD, specifically BMI, waist circumference, systolic blood pressure, total and HDL cholesterol, ratio of total to HDL cholesterol, and type 2 diabetes. Reductions from baseline to follow-up were significant for waist circumference (n=56; 98.3 cm (SD 1.8) to 96.4 cm (SD 1.8), $p=0.04$), HDL cholesterol (1.01 mmol/L (SD 0.03) to 1.11 mmol/L (SD 0.04), $p=0.001$), and ratio of total to HDL cholesterol (5.7 (SD 0.2) to 5.0 (SD 0.2),

p<0.001). Non-significant changes were reported for BMI (n=56; 27.3 (SD 0.9) to 27.3 (SD 0.8), p=0.81), systolic blood pressure (128 mmHg (SD 2.6) to 124 mmHg (SD 3.0), p=0.2), and total cholesterol (5.5 mmol/L (SD 0.2) to 5.3 mmol/L (SD 0.2), p=0.07). Type 2 diabetes status remained constant from baseline to follow-up.

Further, Burgess et al. assessed difference in absolute 5- and 10-year CVD risk. They first calculated the expected risk at follow-up calculated by modifying only age, and compared it to the observed risk. Expected 5-year risk was 4.6% (0.4), and the observed risk was 3.6% (0.4), and the 1.0% (SD 0.4) difference was significant (p<0.001). Similarly, the expected 10-year risk was 10.2% (SD 0.8), and the observed risk was 8.2% (SD 0.7), with a difference of 2.0% (SD 0.7) was significant (p=0.004).

5.5 Subgroup

The subgroup of interest for this systematic review are those determined to be at high risk for the predicted health outcome. Four studies demonstrated the difference in effect between low and high risk groups.

Sorensen et al. compared to the prescription of antiplatelets, lipid-lowering and antihypertensive medications between patients at low-risk (<5% 10-year cardiovascular mortality risk) with patients at high-risk (≥5% 10-year cardiovascular mortality risk). They found that a high risk scores were associated with a 3-fold greater likelihood of being prescribed lipid lowering agents (OR 2.9; 95% CI 1.6, 5.5; p<0.0008), an almost 3.5-fold greater likelihood of being prescribed antihypertensive treatment (OR 3.4; 95% CI 1.9, 6.0; p<0.0001), and a 2-fold greater likelihood of being prescribed antiplatelet medication (OR 2.3; 95% CI 0.8, 6.6; p=0.14).

Chang et al. found that absolute risk reduction (-0.54%, 95% CI -0.93, -0.15) for participants with high risk (20% or greater) was not significantly greater than those with moderate risk (10% to 20%: -0.34%, 95% CI -0.44, -0.24) or low risk (<10%: -0.14%, 95% CI -0.16, -0.12).

Vagholkar et al. examined prescription of medications (antihypertensives, lipid-lowering, or both), treatment intensification, and treatment reduction between low, moderate, or

high risk groups and between intervention and control patients. Both between- and within-group analyses showed no significant differences in the 12-month medication proportions and changes in therapy.

Mehta et al. examined the prescription of both antihypertensive and lipid-lowering medications amongst patients at baseline and six month follow-up periods for up to three years within the low (<10%), moderate (10-14%) and high risk (≥15%) strata. Dispensing rose most sharply in the six month period following baseline and implementation of the intervention, and differed between risk strata.

5.6 Conclusion

In conclusion, many studies examining the impact of risk prediction model use on physician behaviour, patient behaviour, and patient health outcomes found that there were some improvements. The majority of studies identified a significant increase in prescription of preventive medications; changes not found to be statistically significant may still be clinically relevant. Several unique outcomes were categorized as patient behaviour. Though some studies identified an effect of prediction model use on patient behaviour, overall the outcome was too heterogenous to determine whether or not an impact exists. Lastly, though few studies examined event rates, several identified improvements in soft outcomes such as blood pressure or total cholesterol, indicating that risk prediction model use may ultimately result in some improvements in patient health outcomes. The following chapter will present the results of the quantitative assessment, or the meta-analysis, of the data.

Chapter 6

6.0 Meta-analysis

In this chapter, the results of the meta-analyses are presented. Though as a whole, numerous forms of model impact were described in the systematic review, only five outcomes were found to be meta-analyzable: 1) new prescription with antihypertensive medications, 2) new prescription with lipid-lowering medication, 3) smoking cessation, 4) absolute changes in systolic blood pressure, and 5) absolute changes in diastolic blood pressure. Two main types of data were concluded to be appropriate for meta-analysis: dichotomous data, or the number of events and non-events, and continuous data, or changes in mean values. As such, the two summary effect measures calculated for this study were summary odds ratios and standardized mean differences. Studies reporting on similar outcomes were combined in a summary effect measure and visually depicted using a forest plot. Lastly, the results of the risk of bias assessment using the Downs and Black tool are presented.

6.1 Results of individual studies

This systematic review and meta-analysis sought to address what the impact of risk prediction models was on: 1) practitioner behaviour, 2) patient behaviour, and 3) patient health outcomes. Upon completion of the systematic review, five outcomes were identified as being appropriate for the conduct of a meta-analysis as per the three main study objectives. Changes in practitioner behaviour (defined as prescription of antihypertensive or lipid-lowering medications) were found in four studies, patient behaviour change (expressed as smoking cessation) was found in four studies, and patient health outcomes (defined as changes in blood pressure (both systolic and diastolic)) were found in five studies.

6.2 Physician prescribing patterns

The meta-analyses for the outcomes of new prescriptions with antihypertensive and lipid-lowering medications from baseline to follow-up are presented below.

6.2.1 New prescriptions with antihypertensives

Four studies reported the changes in prescription with antihypertensives in patients following the use of a prediction model; the information presented in each study is displayed in Table 8.

Table 8. Reported changes in proportions of patients prescribed with antihypertensive medications from baseline to follow-up in both the intervention and control group.

	Intervention		Control	
Author (year)	Baseline	Follow-up	Baseline	Follow-up
Chang (2016)	1424/29672	2938/29672	1964/109116	4801/109116
Jiao (2015)	6637/9094	7112/8892	6673/9094	6493/8542
Jiao (2014)	833/1072	871/1072	818/1072	852/1072
Vagholkar (2014)	136/475	148/475	133/431	148/431

For the purposes of the meta-analysis, the number of events and non-events in both arms of the studies were required. To derive the number of events, the difference between the number of patients at follow-up prescribed antihypertensives was subtracted by the number of patients prescribed antihypertensives at baseline (Table 9).

Table 9. The calculated number of events (new prescription with an antihypertensive medication) from baseline to follow-up in both the intervention and control group.

	Intervention		Control	
Author (year)	Follow-up — baseline	Number of events	Follow-up — baseline	Number of events
Chang (2016)	2938 - 1424	1514	4801 – 1964	2837
Jiao (2015)	7112 - 6637	475	6493 – 6673	-180
Jiao (2014)	871 - 833	38	852 – 818	34
Vagholkar (2014)	148 - 136	12	148 – 133	15

The number of non-events was calculated by subtracting the number of total participants per treatment arm by the number of events (Table 10). Of particular note is Jiao et al. (2015) where both the intervention and control arms experienced some attrition. When calculating the number of events, the method of calculating the number of events in tandem with the loss to follow-up results in a number of -180. This poses a significant problem for the interpretation and analysis of the data; this value would be interpreted as 180 negative events and not fall within the confines of event or non-event.

The conduct of a complete case analysis was used to account for attrition as recommended by the Cochrane Handbook, ultimately ameliorating the issue of negative events.[190] The complete case analysis was conducted using the methods proposed by Akl et al.[224] A complete case analysis seeks to exclude patients for whom data are missing at follow-up, therefore only analyzing data from patients with available data, followed by a sensitivity analysis using both the best and worst case scenarios where all patients with missing data are classified as either events or non-events. This creates a range of possible effect sizes, accounting for the range of uncertainty. First, the complete case analysis will be presented, followed by the worst- and best-case analysis.

To conduct a complete case analysis, Akl et al. recommends using the following equation:

$$\frac{Events}{[Patients]\ randomized - [patients]\ with\ missing\ outcome\ data}$$

The formula applies to both the intervention and control arm. To provide a measure of events and non-events, attrition was first accounted for. Firstly, in the intervention arm at baseline, approximately 72.98% of patients were prescribed antihypertensive medications (6637/9094). Two hundred and two patients were lost to follow-up. Assuming non-differential attrition, this indicates that of the 202 patients lost, 72.98% (~147 patients) were those who were prescribed antihypertensive medications, and thus 55 patients were not. Subtracting 147 from the previously stated baseline number (6637) and subtracting the full 202 from the denominator (9094), a new prevalence, accounting for attrition, of baseline antihypertensive medication prescription is established (6490/8892). The same method of accounting for attrition was used for the control arm, resulting in a new prevalence of baseline antihypertensive medication prescription (6268/8542).

The calculation of events was completed by subtracting the original follow-up count of patients prescribed with antihypertensives by the new baseline count of patients prescribed. The number of non-events were calculated by using the denominator of the equation as per Akl et al.:

$$Intervention\ arm\text{:}\ \frac{6637 - 6490}{9094 - 202} = \frac{147}{8892}$$

$$Control\ arm\text{:}\ \frac{6493 - 6268}{9094 - 552} = \frac{225}{8542}$$

The values for the denominator represent the total number of participants for whom data is complete. When calculating the number of non-events, this was the value used as the number of total participants as per a complete case analysis. The number of non-events for each study is presented below (Table 10).

Table 10. The calculated number of non-events (no new prescription with antihypertensive medication) using a complete case analysis for both the intervention and control group.

	Intervention		Control	
Author (year)	Total number – number of events	Number of non-events	Total number – number of events	Number of non-events
Chang (2016)	29672 - 1514	28158	109116 – 2837	106279
Jiao (2015)	8892 – 147	8745	8542 – 225	8317
Jiao (2014)	1072 – 38	1034	1072 – 34	1038
Vagholkar (2014)	475 – 12	463	431 – 15	416

The calculated numbers allow us to establish the number of events and non-events, allowing for the conduct of a meta-analysis (Table 11).

Table 11. The number of events and non-events for the intervention and control groups of the studies eligible for meta-analysis.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	1514	28158	2837	106279
Jiao (2015)	147	8745	225	8317
Jiao (2014)	38	1034	34	1038
Vagholkar (2014)	12	463	15	416

The meta-analysis was conducted using a random-effects model as opposed to a fixed-effects model to account for the variations in effect size between studies, allowing us to account for the heterogeneity when comparing the studies. A correction factor of 0.5 was used to account for any zero values. Given the discordant odds ratio in Jiao et al. (2015), a concurrent sensitivity analysis was also employed allowing us to derive the overall

summary effect measure in addition to the summary effect measure excluding Jiao et al. (2015). The results of the meta-analysis are presented below (Figure 3).

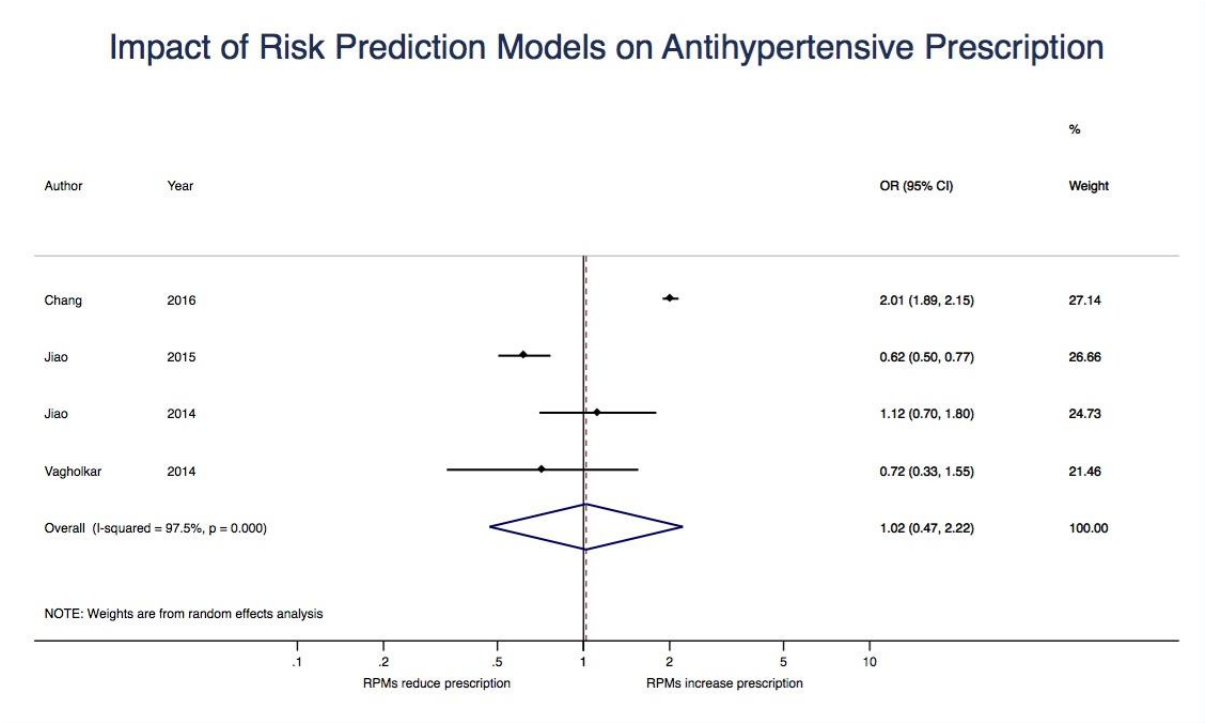

Figure 4. Forest plot depicting the impact of risk prediction models on new prescription with antihypertensive medications.

The overall summary effect indicates that the odds of prescribing are 1.02 times greater (95% CI 0.47, 2.22) in the prediction model group. The confidence interval spans the null value (1.0), and thus the effect is considered statistically non-significant.

6.2.1.1 Sensitivity analysis

The effect size for Jiao et al. (2015) essentially assumes that all the attrition (in both the treatment and control groups) constituted participants who represented non-events. The result of this is striking particularly in the control group, where the assumption of zero events leads to an infinite estimated effect size (made finite through smoothing). As recommended by the Cochrane Handbook, a sensitivity analysis was conducted to provide a range of values to account for the missing data in using a method referred to as the 'best-case" and "worst-case" scenarios. The best-case scenario is where all intervention patients with missing data are inferred to have experienced the event, and

those in the control group with missing data are inferred to not have experienced the event. The inverse would then be labelled the worst-case scenario. Only one study (Jiao et al., 2015) reported attrition. The calculated events and non-events for both the best- and worst-case scenarios are presented below (Table 12).

Table 12. The absolute frequencies as per the best- and worst-case scenarios to account for attrition and allow for the conduct of sensitivity analyses for Jiao et al. 2015.

Scenario	Group	Type of event	Absolute frequency
Best-case	Intervention	Events	675
		Non-events	8419
	Control	Events	0
		Non-events	9094
Worst-case	Intervention	Events	475
		Non-events	8619
	Control	Events	372
		Non-events	8722

Using the number of events and non-events as per the best- and worst-case scenarios for the Jiao et al. (2015) study, we find that the study presents with an odds ratio range from 1.29 (95% CI 1.12, 1.48) to 1459.31 (95% CI 91.17, 23358.39), and an overall summary effect range from 1.34 (95% CI 0.92, 1.94, I^2 = 93.0%, p<0.001) to 3.29 (95% CI 0.77, 14.16, I^2 = 96.7%, p<0.001). Full forest plots are provided in Appendix H.

6.2.1.2 Subgroup analysis: Antihypertensive medication naïve patients

The previous analysis assessing the impact of prediction models on new prescription with antihypertensive medications was conducted on the entire sample. It included patients for whom the event had already occurred. A subgroup analysis was conducted to address the impact of prediction models amongst antihypertensive medication naïve patients (i.e. patients who were not prescribed antihypertensive medications at baseline).

The number of events, or new prescription with antihypertensives, remained constant as previously derived. The number of non-events is given by the number of patients randomized to the intervention group *who are not taking antihypertensives at baseline* and who do not receive a new prescription. The number of non-events was calculated by first subtracting the total number of participants by those who were taking antihypertensive medications at baseline, and then subtracting that figure by the number of events. For example, in Chang et al. (2016), the intervention arm had 29,672 patients, 1424 patients taking antihypertensives at baseline, and a total number of events of 1514. Through simple subtraction, the number of non-events was calculated to be 26734, as demonstrated here:

$$Number\ of\ non-events: 29672 - 1424 - 1514 = 26734$$

To conduct a complete case analysis and account for the loss to follow-up in the Jiao et al. (2015) study, the number of non-events was calculated using the modified baseline numbers that account for attrition. The number of non-events was then calculated using the same methods used for the other studies, as follows:

$$Non-events_{intervention}: 8892 - 6490 - 147 = 2255$$

$$Non-events_{control}: 8542 - 6268 - 225 = \ 2049$$

Inputting all the values into a table allows us to conduct a subgroup analysis in STATA (Table 13). The results of the meta-analysis are presented in Figure 4.

Table 13. The number of events and non-events from baseline to follow-up in both the intervention and control groups amongst patients who were antihypertensive medication naïve at baseline.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	1514	26734	2837	104315
Jiao (2015)	147	2255	225	2049
Jiao (2014)	38	201	34	220
Vagholkar (2014)	12	327	15	283

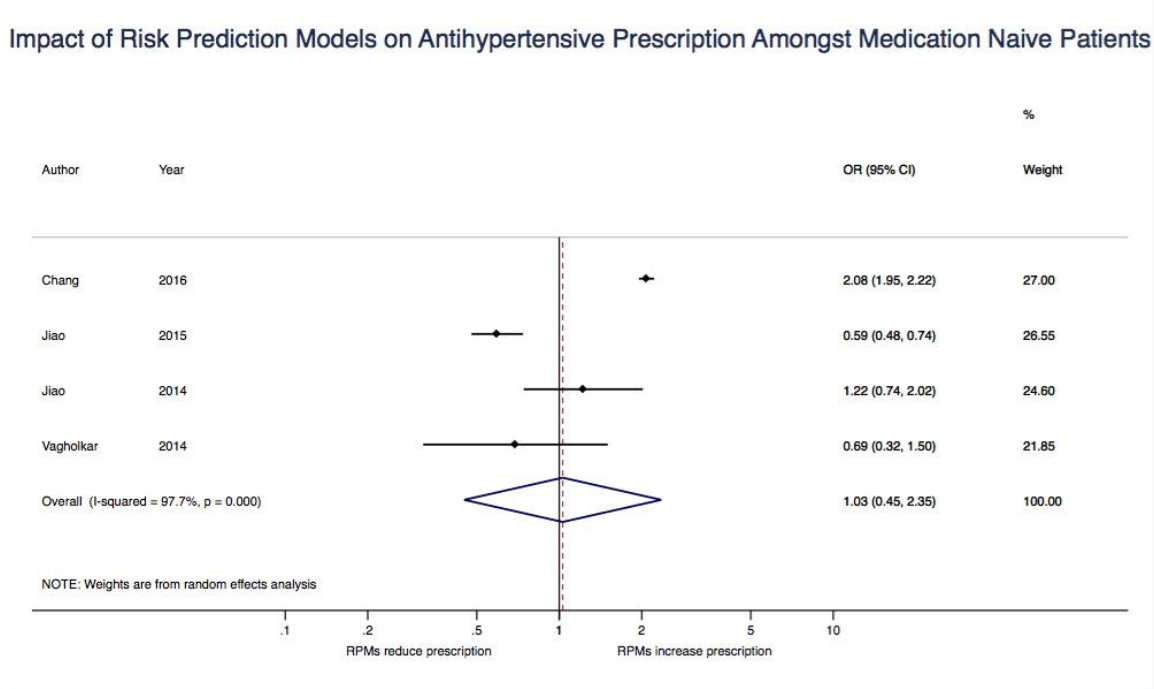

Figure 5. Forest plot depicting the impact of risk prediction models on new prescriptions with antihypertensive medications amongst antihypertensive medication naive patients.

Therefore, amongst patients who were antihypertensive medication naïve, the odds of prescription with an antihypertensive medication was 1.03 times greater (95% CI 0.45,2.35) amongst those who received the intervention than those who did not.

6.2.2 New prescriptions with lipid-lowering medications

The same methods employed in section 6.2.1 were used to derive the number of events and non-events for new prescription with lipid-lowering medication. Four studies were determined to be eligible for the conduct of a meta-analysis. The information presented in each article is displayed in Table 14.

Table 14. Reported changes in proportion of patients prescribed with lipid-lowering medications at baseline and follow-up in both the intervention and control group.

	Intervention		Control	
Author (year)	Baseline	Follow-up	Baseline	Follow-up
Chang (2016)	2878/29672	4540/29672	3383/109116	4691/109116
Jiao (2015)	1189/9094	4551/8892	1225/9094	3903/8542
Jiao (2014)	866/1072	935/1072	880/1072	949/1072
Vagholkar (2014)	101/475	108/475	120/431	130/431

The derived number of events and non-events was calculated in the same manner as in section 6.2.1 (“New prescription with antihypertensives”), and the values are presented in Table 15, which were subsequently used to conduct the meta-analysis (Figure 5).

Table 15. The number of events and non-events for the intervention and control groups of the studies eligible for meta-analysis.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	1662	28010	1308	107808
Jiao (2015)	3388	5504	2752	5790
Jiao (2014)	69	1003	69	1003
Vagholkar (2014)	7	468	10	421

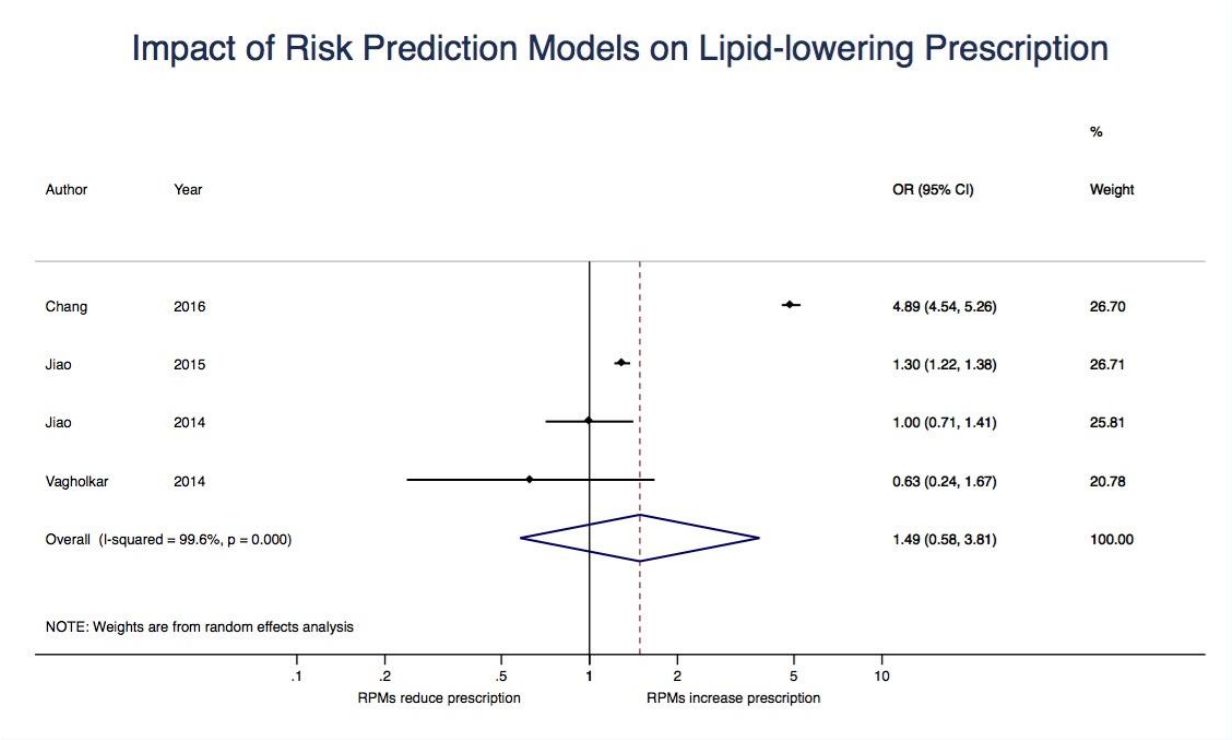

Figure 6. Forest plot depicting the impact of risk prediction models on new prescription with lipid-lowering medications.

Therefore, the overall summary effect measure indicates that the odds of new prescription with lipid-lowering medications is 1.49 times greater (95% CI 0.58, 3.81) amongst patients who received the intervention compared to those that did not.

6.2.2.1 Sensitivity analysis

A sensitivity analysis as per the best- and worst-case scenario method was conducted as per the figures presented in Table 16.

Table 16. The absolute frequencies as per the best- and worst-case scenarios to account for attrition and allow for the conduct of sensitivity analyses for Jiao et al. 2015.

Scenario	Group	Type of event	Absolute frequency
Best-case	Intervention	Events	3564
		Non-events	5530
	Control	Events	2678
		Non-events	6416
Worst-case	Intervention	Events	3362
		Non-events	5732
	Control	Events	3230
		Non-events	5864

Using the number of events and non-events as per the best- and worst-case scenarios for the Jiao et al. (2015) study, we find that the study presents with an odds ratio range from 1.06 (95% CI 1.00, 1.13) to 1.54 (95% CI 1.45, 1.64). The summary effect range is from 1.40 (95% CI 0.48, 4.05, I^2 = 99.7%, p<0.001) to 1.58 (95% CI 0.69, 3.63, I^2 = 99.5%, p<0.001). Full forest plots are provided in Appendix I.

6.2.2.2 Subgroup analysis

The subgroup assessed for with regards to lipid-lowering medications was new prescriptions with lipid-lowering medications amongst those that are medication naïve. The number of events and non-events was calculated similarly to section 6.2.2. The calculated figures are presented below (Table 17). The results of the corresponding meta-analysis are presented below (Figure 6).

Table 17. The number of events and non-events from baseline to follow-up in both the intervention and control groups amongst patients who were lipid-lowering medication naïve at baseline.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	1662	25132	1308	104425
Jiao (2015)	3388	4341	2752	4639
Jiao (2014)	69	137	69	123
Vagholkar (2014)	7	367	10	301

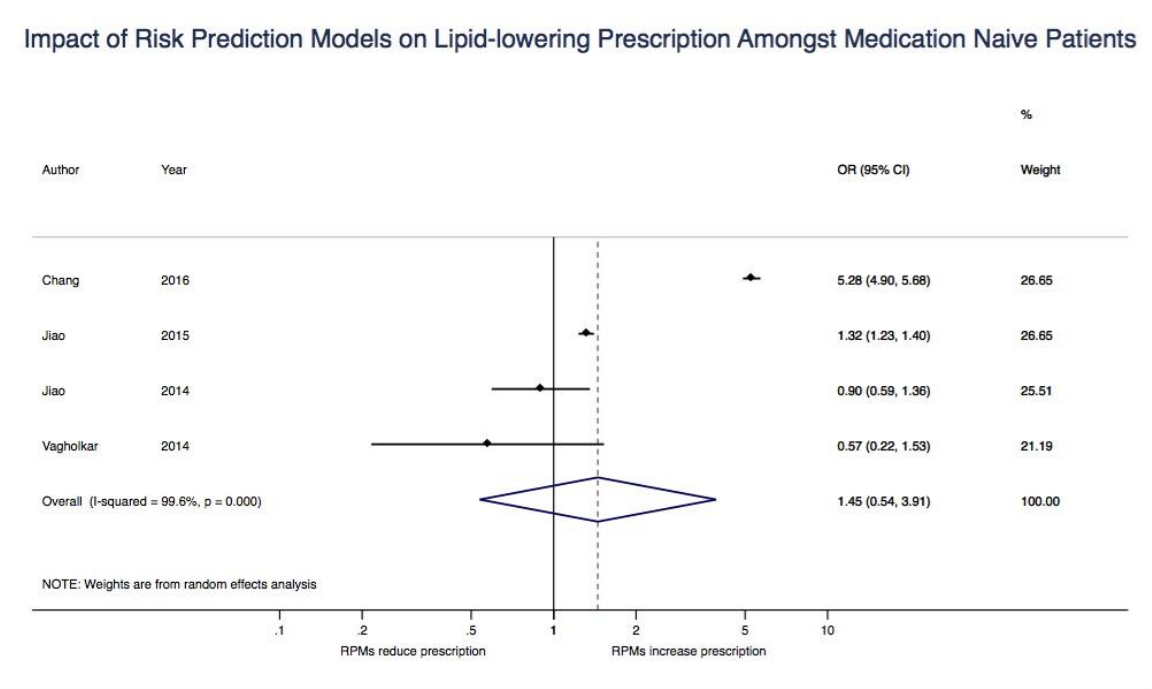

Figure 7. Forest plot depicting the impact of risk prediction models on new prescription with lipid-lowering medications amongst medication naive patients.

Overall, it was found that the odds of new prescription with lipid-lowering medication amongst medication naïve patients favoured the intervention (OR 1.45, 95% CI 0.54, 3.91), though the result was statistically non-significant.

6.3 Patient behavioral outcomes

Though several articles assessed for patient behavioural outcomes as a result of prediction model use, including changes in physical activity and diet, or continuity of care, there were only a sufficient number of studies to conduct a meta-analysis for smoking cessation.

6.3.1 Smoking cessation

Four studies reported baseline and follow-up proportions of smokers in both the intervention and control groups. The information presented in the articles is displayed below (Table 18).

Table 18. Reported changes in proportions of smokers from baseline to follow-up in both the intervention and control groups.

	Intervention		Control	
Author (year)	Baseline	Follow-up	Baseline	Follow-up
Chang (2016)	5311/29672	4837/29672	24224/109116	22692/109116
Jiao (2015)	927/9094	346/8892	906/9094	235/8542
Lowensteyn (1998)	42/202	39/202	21/89	19/89
Powers (2011)	8/44	6/44	8/45	8/45

Similar to the previous two outcomes (prescription with antihypertensive and lipid-lowering medications), the number of events and non-events was calculated. Events were defined as patients who had quit smoking from baseline to follow-up. The method of calculating the number of events differed from the previous two dichotomous outcomes in that the event of smoking cessation decreases the number from baseline to follow-up, while prescription with antihypertensive or lipid-lowering medications increases the number from baseline to follow-up. Hence, as opposed to the calculation of events used previously (follow-up – baseline), the difference from baseline to follow-up was used to calculate the number of events (Table 19). Note that again for Jiao et al. (2015), the

baseline numbers were modified to account for attrition, resulting in baseline proportions of smokers of 906/8892 in the intervention arm and 851/8542 in the control arm.

Table 19. The calculated number of events (i.e. number of patients who quit smoking) from baseline to follow-up in both the intervention and control groups.

	Intervention		Control	
Author (year)	Baseline – follow-up	Number of events	Baseline – follow-up	Number of events
Chang (2016)	5311 – 4837	474	24224 – 22692	1532
Jiao (2015)	906 – 346	560	851 – 235	616
Lowensteyn (1998)	42 – 39	3	21 – 19	2
Powers (2011)	8 – 6	2	8 – 8	0

Calculating the number of non-events was conducted in the same fashion as in previous examples, where the total number of participants was subtracted by the number of events (Table 20).

Table 20. The calculated number of non-events from baseline to follow-up in both the intervention and control groups.

	Intervention		Control	
Author (year)	Total number – number of events	Number of non-events	Total number – number of events	Number of non-events
Chang (2016)	29672 - 474	29198	109116 – 1532	107584
Jiao (2015)	8892 – 560	8332	8542 – 616	7926
Lowensteyn (1998)	202 – 3	199	89 – 2	87
Powers (2011)	44 – 2	42	45 – 0	45

Compiling the list of events and non-events for smoking behaviour allows us to conduct a meta-analysis (Table 21; Figure 7).

Table 21. The number of events and non-events for the intervention and control groups of the studies eligible for meta-analysis.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	474	29198	1532	107584
Jiao (2015)	560	8332	616	7926
Lowensteyn (1998)	3	199	2	87
Powers (2011)	2	42	0	45

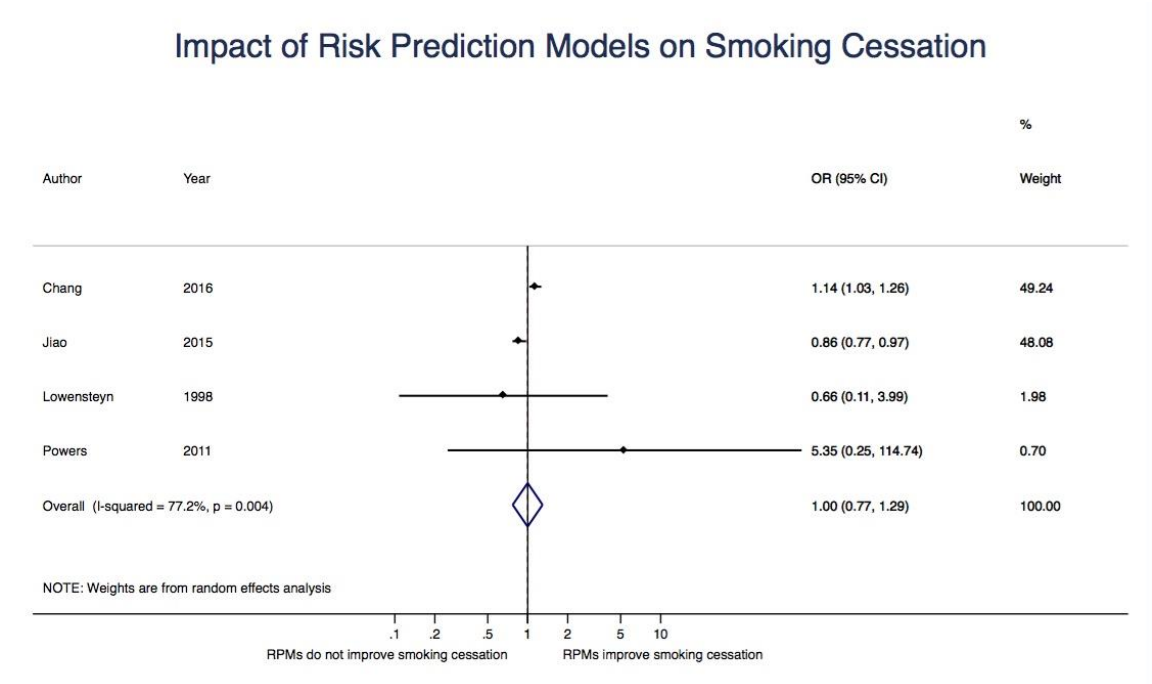

Figure 8. Forest plot depicting the impact of risk prediction models on smoking cessation.

Overall, there appeared to be no impact of risk prediction model use on the patient behaviour of smoking cessation when examining all participants (OR 1.00, 95% CI 0.77, 1.29).

6.3.1.1 Sensitivity analysis

A sensitivity analysis to provide a range of potential effect values accounting for the attrition in Jiao et al. (2015) was conducted using the best- and worst-case scenarios, as previously described in section 6.2.1.1. The values used are presented below (Table 22).

Table 22. The absolute frequencies as per the best- and worst-case scenarios to account for attrition and allow for the conduct of sensitivity analyses for Jiao et al. 2015.

Scenario	Group	Type of event	Absolute frequency
Best-case	Intervention	Events	581
		Non-events	8513
	Control	Events	119
		Non-events	8980
Worst-case	Intervention	Events	379
		Non-events	8715
	Control	Events	671
		Non-events	8423

Using the numbers of events and non-events as per the best- and worst-case scenarios for the Jiao et al. (2015) study, we find that the study presents with an odds ratio range from 0.55 (95% CI 0.48, 0.62) to 5.15 (95% CI 4.22, 6.29), and an overall summary effect range from 0.84 (95% CI 0.43, 1.63, I^2 = 96.1%, $p<0.001$) to 2.04 (95% CI 0.59, 6.97, I^2 = 98.3%, $p<0.001$). Full forest plots are provided in Appendix J.

6.3.1.2 Subgroup analysis: Smoking cessation amongst smokers

The number of non-events in the previous section includes non-smoking patients, allowing us to estimate the impact of prediction models on smoking behaviour in the population. To garner a sense of the impact of prediction models on smoking cessation amongst smokers, a subgroup analysis was conducted. Similar to the previous subgroup analyses, the number of events remained constant, while the number of non-events excluded non-smokers. The completed number of events and non-events is presented below (Table 23). The results of the meta-analysis are presented in Figure 8.

Table 23. The number of events and non-events from baseline to follow-up in both the intervention and control groups amongst patients who were smokers at baseline.

	Intervention		Control	
Author (year)	Events	Non-events	Events	Non-events
Chang (2016)	474	4837	1532	22692
Jiao (2015)	560	346	616	235
Lowensteyn (1998)	3	39	2	19
Powers (2011)	2	6	0	8

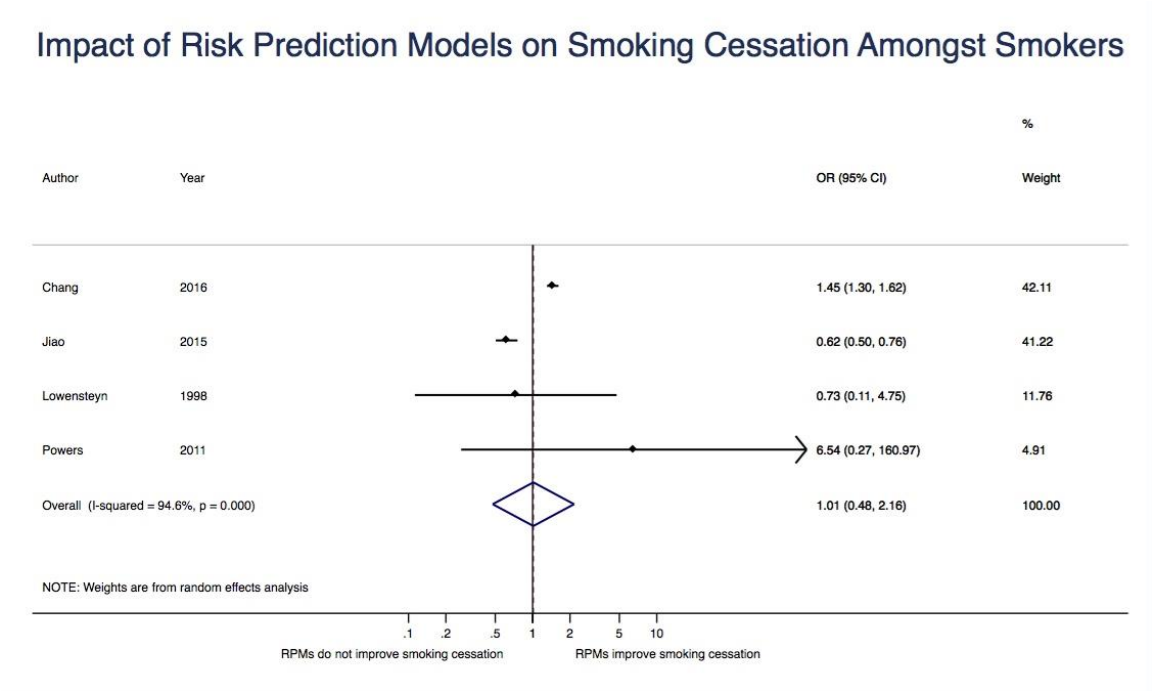

Figure 9. Forest plot depicting the impact of risk prediction models on smoking cessation amongst smokers.

When examining smokers, there appears to be no impact of risk prediction model use on smoking cessation (OR 1.01, 95% CI 0.46, 2.18).

6.4 Changes in systolic blood pressure

Four studies identified through the systematic review process assessing the impact of prediction models on changes in systolic blood pressure were identified as being appropriate for a meta-analysis. Table 24 displays the information presented in each article.

Table 24. The reported changes in systolic blood pressure from baseline to follow-up in both the intervention and control groups. Mean and absolute change values are presented in mmHg; parenthesized values are the reported standard deviations.

	Intervention				Control			
Author (Year)	Sample size	Baseline mean	Follow-up mean	Absolute change	Sample size	Baseline mean	Follow-up mean	Absolute change
Chang (2016)	29672	131.9 (17.4)	130.0 (12.7)	NA	109116	128.5 (13.6)	129.3 (11.3)	NA
Jiao (2015)	9094	135.41 (17.05)	130.12 (14.68)	NA	9094	135.45 (16.56)	132.35 (15.51)	NA
Lowensteyn (1998)	202	133.0 (15.8)	NA	-2.0 (14.2)	89	129.2 (15.5)	NA	-1.2 (14.1)
Powers (2011)	44	128.4 (2.7)	128.2 (2.9)	NA	45	126.0 (2.7)	125.0 (2.8)	NA

Three of the four studies did not report the absolute change in SBP from baseline to follow-up. The sample mean difference (D), otherwise referred to as the absolute change, was calculated by subtracting the baseline mean ($\bar{x}_1$) by the follow-up mean ($\bar{x}_2$) in studies where only the baseline and follow-up means were provided. Using the equation:

$$D = \bar{x}_1 - \bar{x}_2,$$

the absolute change in SBP was calculated for both the intervention and control groups (Table 25).

Table 25. The calculation of absolute change in systolic blood pressure from baseline to follow-up in both the intervention and control groups.

	Intervention		Control	
Author (year)	$\bar{x}_1 - \bar{x}_2$	Absolute change	$\bar{x}_1 - \bar{x}_2$	Absolute change
Chang (2016)	131.9 – 130.0	1.9	128.5 – 129.3	-0.8
Jiao (2015)	135.41 – 130.12	5.29	135.45 – 132.35	3.1
Powers (2011)	128.4 – 128.2	0.2	126.0 – 125.0	1.0

In order to calculate the standard deviation of the difference, the following equation as per Borenstein et al. was applied:

$$S_{diff} = \sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$$.[194]

The correlation coefficient, *r*, was not provided. Using the Cochrane Handbook for Systematic Reviews of Interventions, *r* was imputed based on the absolute change for SBP and DBP as calculated by Lowensteyn et al. based on the equation:

$$r = \frac{S_{baseline}^2 + S_{final}^2 - S_{change}^2}{2 \times S_{baseline} \times S_{final}}$$.[190,213]

The article by Lowensteyn et al. only provided the standard deviation *S* for the baseline SBP and the absolute change. However, as per the Cochrane Handbook, "Where either the baseline or final standard deviation is unavailable, then it may be substituted by the other, provided it is reasonable to assume that the intervention does not alter the variability of the outcome measure" (p. 487).[190] Therefore, the final SBP standard deviation was substituted by the baseline standard deviation. Thus, the correlation coefficient values for the intervention and control groups were calculated as follows:

$$r_{intervention} = \frac{15.8^2 + 15.8^2 - 14.2^2}{2 \times 15.8 \times 15.8} \sim 0.60$$

$$r_{control} = \frac{15.5^2 + 15.5^2 - 14.1^2}{2 \times 15.5 \times 15.5} \sim 0.59$$

Because the correlation coefficient values are greater than 0.5, it is indicated that assessing the change score from baseline to follow-up provides greater value and precision than analyzing the final values of blood pressure. The calculated *r* was imputed to calculate the standard deviation of the absolute change in SBP for the additional three studies (Table 26).

Table 26. The calculated standard deviation of the absolute change in systolic blood pressure from baseline to follow-up in both the intervention and control groups using the imputed correlation coefficient values derived from Lowensteyn et al.

	Intervention		Control	
Author (year)	$\sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$	S_{diff}	$\sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$	S_{diff}
Chang (2016)	$\sqrt{17.4^2 + 12.7^2 - 2 \times 0.6 \times 17.4 \times 12.7}$	14.10	$\sqrt{13.6^2 + 11.3^2 - 2 \times 0.59 \times 13.6 \times 11.4}$	11.39
Jiao (2015)	$\sqrt{17.05^2 + 14.68^2 - 2 \times 0.6 \times 17.05 \times 12.}$	15.70	$\sqrt{16.56^2 + 15.51^2 - 2 \times 0.59 \times 16.56 \times 15.5}$	14.55
Powers (2011)	$\sqrt{2.7^2 + 2.9^2 - 2 \times 0.6 \times 2.7 \times 2.9}$	2.51	$\sqrt{2.7^2 + 2.8^2 - 2 \times 0.59 \times 2.7 \times 2.8}$	2.49

Completing the initial table (Table 27) provides the data necessary required to conduct a meta-analysis comparing the mean difference in systolic blood pressure from baseline to follow-up between the intervention and control groups (Figure 9).

Table 27. The absolute change values in standard deviation (mmHg) and associated standard deviations for both the intervention and control groups.

	Intervention			Control		
Author (Year)	Sample size	Absolute change	Standard deviation	Sample size	Absolute change	Standard deviation
Chang (2016)	29672	-1.9	14.10	109116	0.8	11.39
Jiao (2015)	9094	-5.29	15.70	9094	-3.1	14.55
Lowensteyn (1998)	202	-2.0	14.20	89	-1.2	14.10
Powers (2011)	44	-0.2	2.51	45	-1.0	2.49

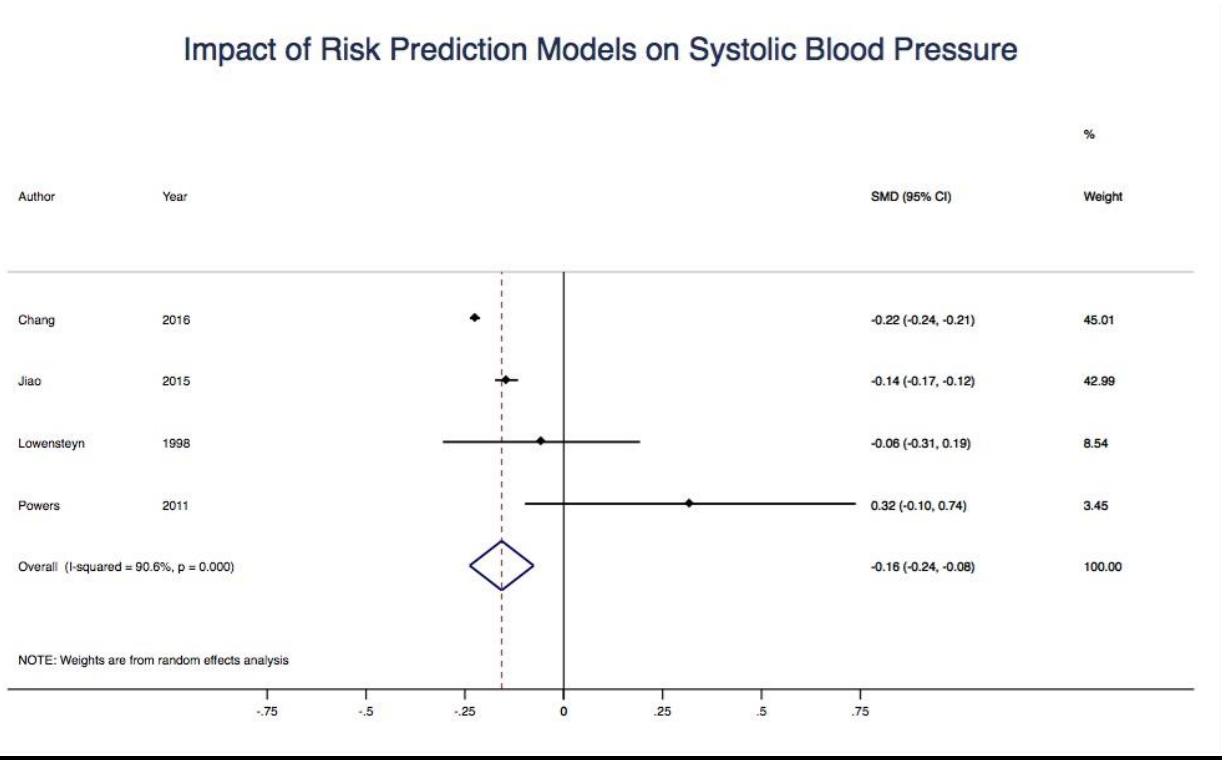

Figure 10. Forest plot depicting the impact of risk prediction models on absolute changes in systolic blood pressure.

The forest plot indicates that overall, the absolute change of systolic blood pressure is 0.16 mmHg (95% CI -0.24, -0.08) lower in patients who receive the intervention compared to those who do not.

6.5 Changes in diastolic blood pressure

Similarly, four studies were identified that were considered to be appropriate for meta-analysis for changes in diastolic blood pressure (DBP). Table 28 presents the information provided in each of these four studies.

Table 28. The reported changes in diastolic blood pressure from baseline to follow-up in both the intervention and control groups. Mean and absolute change values are presented in mmHg; parenthesized values are the reported standard deviations.

	Intervention				Control			
Author (Year)	Sample size	Baseline mean	Follow-up mean	Absolute change	Sample size	Baseline mean	Follow-up mean	Absolute change
Chang (2016)	29672	80.2 (10.5)	78.5 (7.7)	NA	109116	78.7 (8.2)	78.7 (6.7)	NA
Jiao (2015)	9094	75.11 (10.34)	71.6 (10.26)	NA	9094	75.08 (9.77)	73.23 (9.72)	NA
Lowensteyn (1998)	202	82.3 (10.2)	NA	0.9 (8.1)	89	79.8 (11.2)	NA	-0.1 (9.8)
Powers (2011)	44	73.5 (1.9)	74.9 (2.0)	NA	45	76.6 (1.8)	76.7 (1.9)	NA

The absolute change in DBP was calculated for the three articles that did not present them using the formula as presented in section 6.4 (Table 29).

Table 29. The calculation of absolute change in diastolic blood pressure from baseline to follow-up in both the intervention and control groups.

	Intervention		Control	
Author (year)	$\bar{x}_1 - \bar{x}_2$	Absolute change	$\bar{x}_1 - \bar{x}_2$	Absolute change
Chang (2016)	80.2 – 78.5	1.7	78.7 – 78.7	0
Jiao (2015)	75.11 – 71.6	3.51	75.08 – 73.23	1.85
Powers (2011)	73.5 – 74.9	-1.4	76.6 – 76.7	-0.1

The correlation coefficient (*r*) was calculated for both the intervention and control group using the data presented by Lowensteyn et al., and imputed to calculate the standard deviation of the mean difference (Table 30).

$$r_{intervention} = \frac{10.2^2 + 10.2^2 - 8.1^2}{2 \times 10.2 \times 10.2} \sim 0.68$$

$$r_{control} = \frac{11.2^2 + 11.2^2 - 9.8^2}{2 \times 11.2 \times 11.2} \sim 0.62$$

Table 30. Calculation of the standard deviation of the change in diastolic blood pressure.

	Intervention		Control	
Author (year)	$\sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$	S_{diff}	$\sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$	S_{diff}
Chang (2016)	$\sqrt{10.5^2 + 7.7^2 - 2 \times 0.68 \times 10.5 \times 7.7}$	7.72	$\sqrt{8.2^2 + 6.7^2 - 2 \times 0.62 \times 8.2 \times 6.7}$	6.12
Jiao (2015)	$\sqrt{10.34^2 + 10.26^2 - 2 \times 0.68 \times 10.34 \times 10.26}$	8.24	$\sqrt{9.77^2 + 9.72^2 - 2 \times 0.62 \times 9.77 \times 9.72}$	7.80
Powers (2011)	$\sqrt{1.9^2 + 2.0^2 - 2 \times 0.68 \times 1.9 \times 2.0}$	1.56	$\sqrt{1.8^2 + 1.9^2 - 2 \times 0.62 \times 1.8 \times 1.9}$	1.48

Again, given that *r* exceeds 0.5, we proceeded to conduct the meta-analysis (Figure 10) based on the absolute change in diastolic blood pressure using the figures provided in Table 31.

Table 31. The calculated absolute changes in diastolic blood pressure and associated standard deviations and sample sizes for both the intervention and control groups.

	Intervention			Control		
Author (Year)	Sample size	Absolute change	Standard deviation	Sample size	Absolute change	Standard deviation
Chang (2016)	29672	1.7	7.72	109116	0.0	6.12
Jiao (2015)	9094	3.51	8.24	9094	1.85	7.80
Lowensteyn (1998)	202	0.9	8.1	89	-0.1	9.8
Powers (2011)	44	-1.4	1.56	45	-0.1	1.48

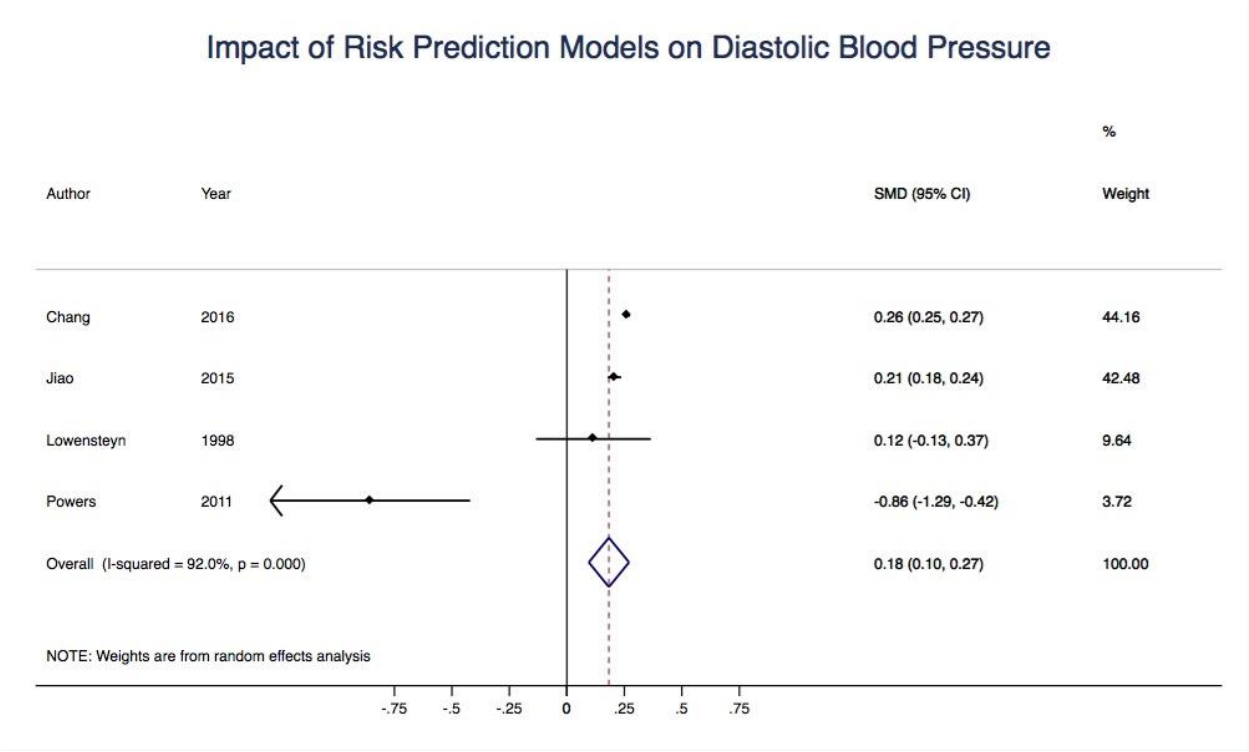

Figure 11. Forest plot depicting the impact of risk prediction models on absolute changes in diastolic blood pressure.

The summary effect measure indicates that patients who receive the intervention experience a 0.18 mmHg (95% CI 0.10, 0.27) greater increase in diastolic blood pressure compared to those who did not.

6.6 Conclusion

The results of the meta-analysis found that risk prediction model use favourably impacts practitioner behaviour, specifically prescription of antihypertensive and lipid-lowering medications, though neither effect was statistically significant. There appeared to be no impact of prediction model use on the patient behaviour of smoking cessation. Lastly, though intervention patients did experience a slight increase in diastolic blood pressure when compared to control patients, there was a small improvement in the patient health outcome of systolic blood pressure, with intervention patients experiencing a statistically significant greater reduction in systolic blood pressure.

Chapter 7

7.0 Discussion

The use of risk prediction models in primary care settings provides an objective, evidence-based estimate of a patient's absolute risk of having (diagnostic) or developing (prognostic) an outcome. Though not intended to replace a physician's clinical judgment, they have the potential to complement the clinical decision-making process. Their incorporation in numerous guidelines indicates a growing movement towards using risk prediction models in routine clinical practice. However, the evidence regarding their impact is sparse and dispersed.

This study sought to collect, collate, and present evidence regarding the impact of chronic disease risk prediction model use in primary care settings on both patient and physician behaviour, and patient health outcomes. Few studies have attempted to define the impact of risk prediction models and the literature remains sparse regarding their effects, necessitating a need for an objective, comprehensive systematic review and meta-analysis to compile the presently available evidence. Through a systematic search of the literature, a narrative summary of the results, and where possible, a meta-analysis of changes in behavioral and health outcomes, the present evidence regarding the impact of risk prediction models is presented, forming a foundation from which future studies examining the impact of prediction models may be conducted.

As far as it is known, this is one of the first systematic reviews and the first meta-analysis addressing the impact of risk prediction model use in primary care settings. Previous systematic reviews have focused primarily on the development and validation of existing models for single health outcomes. For example, Damen et al. sought to provide an overview of existing risk prediction models for CVD.[24] Another systematic review examined the existing models for melanoma incidence, reporting what the possible risk factors were as well as measures of model performance, such as sensitivity and specificity.[225] Of the limited number of studies that have addressed the potential impact of model use, assessments of impact were often conducted secondary to assessments of development or validation.[226,227] Further, no studies were identified that have attempted

to conduct a meta-analysis for clinically relevant outcomes associated with model use in primary care settings.[33] By providing an overview of all identified studies examining the impact of risk prediction models, this systematic review has helped to address this gap in the literature.

This chapter summarizes the results obtained from the systematic review and meta-analysis, discussing possible reasons for any existent or non-existent effects. The strengths and limitations will also be discussed, and where possible, methods for overcoming any limitations will be explored. Lastly, suggestions and guidance for future exploration in this area will be explored.

7.1 Overview of study results

There have been few studies that have examined the impact of risk prediction models in primary care settings for chronic diseases. Though the initial systematic search identified well over 8,000 articles, only 22 studies met the eligibility criteria for this review. Not all the included studies reported on each of the three primary outcomes; most frequently, the impact was assessed for patient health outcomes (77%), followed by physician behaviour (68%) and lastly patient behaviour (50%).

Generally, the evidence does not strongly support the use of risk prediction models for the primary prevention of chronic disease. Physician behaviour appeared to be most strongly affected, with the majority of included studies experiencing some increases in prescription of preventive medications, though the effect becomes non-significant when meta-analyzed. Risk-reducing patient behaviours were the least affected by prediction model use, with few studies indicating a significant effect on changes in physical activity or smoking cessation, and the effect tending towards the null when combined. Lastly, overall event rates for cardiovascular- or diabetes-related health outcomes were only reported in a limited number of study. Though generally it appeared that recipients of the prediction model experienced fewer events, the study samples were highly homogenous, reducing the generalizability of the finding. When examining proxy measures for health outcomes, such as levels of risk factors, though a statistically significant effect was noted for changes in blood pressure (both systolic and diastolic), these results may not have

clinical significance given their small magnitude. The meta-analyses did demonstrate I^2 values ranging from 77.2% to 99.6%, indicating a higher degree of inconsistency of study findings across studies, suggesting heterogeneity between studies. Section 5.3.3 lists the variations in intervention used; though each study used the risk prediction model as a main component of their intervention, some provided relative measures of risk in addition to the absolute measure, the format of risk presentation varied, while others still in a more directive approach provided lifestyle consultations with other healthcare providers. Given the possibility of bias and the heterogeneity present in the meta-analysis, these findings should be interpreted with caution.

7.2 Physician behaviour

Risk prediction models are intended to ultimately improve the health of patients, a goal that is achieved, at least in part, through modification of the providers' behaviour. The prescription of preventive medications, a form of physician behaviour, is indicated for patients at high risk of disease as they may reduce the patients' absolute risks. The results of this study indicate there may be some changes in physician prescribing patterns. Eleven studies reported the impact of prediction model use on an aspect of physician behaviour, largely changes in prescription patterns. A meta-analysis was only considered appropriate for changes in two medications, namely antihypertensives and lipid-lowering medications. It was found through the meta-analysis that physicians who used a risk assessment tool were more likely to prescribe these medications, though these changes were not statistically significant (Figure 3 and Figure 5). However, the impact of model use on prescribing patterns may still be clinically relevant.

The meta-analysis may have been prone to issues of representativeness; though changes in prescription were identified in nine and ten studies for antihypertensives and lipid-lowering medications respectively, less than half reported data appropriate for a meta-analysis. Indeed, through simple vote counting, increases in antihypertensive prescription were found to be statistically significant in five studies (55.6%), while increases in lipid-lowering medication prescription were found to be significant in six studies (60%). Further, an effect in favour of prediction model use, though not significant, was noted in three additional studies for antihypertensive prescriptions and

four additional studies for lipid-lowering medications. If all the identified studies had data reported allowing for their incorporation in the meta-analysis, it is possible that that a significant change may have been obtained. As it stands, this indicates that the meta-analysis may have been underpowered to detect a significant change in favour of new prescription with preventive medications, and the inclusion of additional studies may lend credence to the belief that risk prediction models positively influence physician behaviour.

The event rates to calculate measures of effect were in many cases extrapolated and may not have been entirely accurate. For example, several participants were already prescribed antihypertensive medications at baseline. The number of events was calculated by subtracting the counts of persons prescribed medication at follow-up by those prescribed at baseline, which may be problematic. For example, if one patient were de-prescribed and two new patients were prescribed during the follow-up period, the arithmetic would conclude that only one new prescription was given, when in reality, two were. Though an unlikely scenario, given the nature of a secondary analysis, it is difficult without the original data to ensure that all prescriptions were amongst new participants. Further, though an available case analysis was used to account for attrition in the meta-analysis, again, without the original data, assumptions were made to estimate the number of events and non-events, namely that the participants that were lost to follow-up did not differ from those that remained in the study. Despite this potential limitation, without the original data, this remains the most appropriate method to account for attrition and calculate the number of events.

This thesis defined physician behaviour primarily as changes in preventive medications, such as antihypertensive or lipid-lowering medications. This was inherently flawed an increase in prescription in and of itself does not necessarily indicate an improvement in clinical patterns. Indeed, a more useful measure of improvements in physician behaviour may have been quantified as the *appropriate* prescription with preventive medications, where medications are given in accordance to clinical guidelines or thresholds of risk. However, there is evidence to suggest preventive medications for chronic diseases are underutilized where recommended.[228,229,230] Given that preventive medications are

under-prescribed, any increases in their prescription may be viewed as beneficial. For greater accuracy in terms of benefits of model use, future studies should draw attention to the appropriateness of prescription with preventive medications rather than adopting an all-encompassing approach.

7.3 Patient behaviour

Patient behaviour outcomes were found to be the most variably examined in model impact analysis studies, with measures used inconsistently across studies. The most common aspect of patient behaviour assessed in this review was smoking cessation, examined in eight studies and most consistently defined, especially when compared to the next most common measure, physical activity, which was assessed in four studies and measured in four different ways. The impact of risk prediction models on these two areas of patient behaviour remains inconclusive. Though some changes in physical activity were noted at the individual study level, it was difficult if not impossible to determine if an effect existed at the review level. Interestingly, though there exists no impact of risk prediction models on smoking cessation in the meta-analysis, at the individual study level, several studies found decreases in smoking prevalence, indicating that there may be an effect but the meta-analysis was underpowered to detect a change. Overall, the evidence does not support that model use has an impact on patient behaviour, but given some effects noted at the study level, this relationship warrants further investigation to more quantitatively and accurately to be determined.

Though there are several health-related behaviours that patients may initiate to reduce their risk of chronic disease, no evidence of impact for risk prediction model use was found on patient behaviour. This relationship, or rather lack thereof, may be understandable. One study examined the clustering of five health-related behaviours (not smoking, engaging in physical activity, consuming no to moderate amounts of alcohol, maintaining normal body weight, and obtaining daily sufficient sleep), finding that amongst US adults, only 6.3% of participants engaged in all of the behaviours, with variations of prevalence for each behaviour.[231] The researchers proposed that the five behaviours were not equal in health consequence or in terms of amenability to intervention, indicating a multifaceted approach through several avenues is necessary to

positively affect changes in individual behaviour.[231] Though several studies included in this review incorporated aspects of lifestyle advice in the intervention (section 5.2.3), the scope of the advice was limited in terms of content and modes of delivery; some only provided a leaflet of information, while only three included verbal consultations with health care professionals. The limited nature of lifestyle intervention may explain, at least in part, why health-related patient behaviours were not found to be affected by prediction model use.

Further, the present body of research assumes equivalence regarding patient perception of risk, though this is not necessarily the case. For example, the acceptable risk of nuclear meltdown through the lens of the public, or the risk at which no further safety improvements are deemed necessary, is often considered to be approximately one in a million.[232] However, this level of acceptable risk is derived from risk perceptions, which encompass not just the probability of the outcome but also the magnitude of harms, the latter which may differ greatly from person to person, affecting individual levels of acceptable risk.[233] Depending on the patient and the physician's level of numeracy, the interpretation of risk may also vary and affect behavioural outcomes.[234] Applied to risk prediction models and measures of absolute risk, the acceptable, or *tolerable*, risk may differ from person to person, with a spectrum of associated behavioural responses ranging from apathy to anxiety with regards to preventive measures, providing a possible explanation for the consequent patient behaviours found in this study.

7.4 Patient health outcomes

One of the primary outcomes of interest of this systematic review and meta-analysis was to assess the impact of risk prediction models on patient health outcomes. The definition of patient health outcomes was intentionally left broad to provide a full spectrum of possible outcomes, from hard outcomes, such as incidence of stroke, to proxies for health outcomes or soft outcomes, such as changes in systolic blood pressure. The studies included in this review focused primarily on changes in absolute risk and changes in risk factor levels. At the individual study level, there was a lack of consistency in terms of the findings. For example, though risk prediction model use is expected to improve a patient's absolute risk of experiencing a chronic disease, decreases in absolute risk were

found in fewer than half the included studies. This trend of uncertainty was consistent across most reported health outcomes, including changes in blood pressure or cholesterol levels.

Several of the studies identified in the systematic review were not considered meta-analyzable given the inconsistency in data reporting. Only two soft outcomes were meta-analyzable: changes in systolic and diastolic blood pressure. The results of the meta-analysis indicate that there is a small but significant decrease in systolic blood pressure. Our results suggest that risk prediction models may have an impact on reducing systolic blood pressure amongst patients, though caution must be used when generalizing the results due to concerns of representativeness, heterogeneity, and the small magnitude of effect; the small decrease in systolic blood pressure may not have any effect on the patient's absolute risk of disease. Interestingly, in terms of diastolic blood pressure, a significant increase was found. Though this may appear to be contradictory given that model use should, theoretically speaking, result in a decrease in diastolic blood pressure, again, this effect should be interpreted cautiously as once again, there exists the potential for unrepresentativeness and the small magnitude of effect may have no impact on absolute risk. In other words, though the changes in blood pressure were statistically significant, given their small magnitude, they may not be clinically significant.

The inconsistency of evidence may be attributed to a few key factors. The pathway from risk prediction model use to changes in patient health outcomes requires changes in behaviour, both physician and patient. Preventive interventions may be enacted by the physician, such as the prescription with preventive medications, with patients making the necessary corresponding changes in health-related behaviours, such as adhering to the medication schedule, but without the health-related behavioural modifications, the impact of model use on health outcomes may be muted. Further, the studies included varied in terms of follow-up periods, possibly not allowing enough time for changes to be noted or at least providing some explanation for heterogeneity in terms of the magnitude of change. Given the novelty of impact analysis studies, future research in the area would benefit from quantifying the impact of model use on behavioural modifications and adopting a consistent length of follow-up period of sufficient time.

Most studies reporting on changes in risk factor values reported baseline and follow-up values without a measure of change. In many circumstances, analyses conducted on the follow-up values can provide a measure of effect assuming that at baseline, both the intervention and control group are equivalent, and therefore, any differences at follow-up are a measure of treatment effect. However, this does not allow us to examine the magnitude of impact. In other words, by providing the baseline and follow-up values, the researchers seek to resolve whether there is any effect of intervention use; by calculating the absolute change from baseline to follow-up, the researchers would be resolving a different question, namely how large is the impact of risk prediction models? Though the two purposes may differ, by only assessing for significant changes in follow-up values, the assumption is that values are the same at baseline, an assumption which may be void in some cases. A measure of statistical "sameness" does not indicate that the values at baseline are identical, but rather that they are similar. A more accurate measure of effect would be to determine whether the absolute change in the intervention and control arm differs, allowing readers to more meaningfully determine if an impact exists, and if so, whether the magnitude is of clinical significance.

7.5 Strengths

There exists a growing movement towards using risk prediction models in clinical settings as indicated by the incorporation of prediction models in several guidelines internationally. However, there exists a lack of evidence regarding the potential impact(s) of the models on clinical practice and on patient health outcomes. This strongly indicates that research is required in this field, a need that has been expressed by several researchers. This study is among the first systematic reviews to extensively examine the literature for studies investigating the impact of chronic disease risk prediction models. This is also the first meta-analysis to quantify the impact of model use on physician behaviour, patient behaviour, and patient health outcomes. As such, this study sought to provide the strongest level of evidence examining the impact of model use.

Though previously conducted systematic reviews have focused specifically on cardiovascular diseases, our eligibility criteria allowed us to expand our scope to include

other chronic diseases, providing a more holistic perspective of the impact of prediction models. Though this study may have identified studies assessing primarily the impact of cardiovascular risk prediction models, this review has identified the need for impact analysis studies of models predictive of other chronic diseases. The Gail model, for example, was developed in 1989, and yet no studies assessing for its impact on breast cancer risk were identified, despite almost 30 years since its inception.[26] In identifying this gap in the literature, future studies may be conducted to further expand the scope of the literature and provide insights regarding model impact for chronic diseases presently unexamined.

7.6 Limitations

There exists the possibility that not all the literature pertaining to model impact was identified. This may be attributable to the lack of database specific terms for concepts such as 'risk prediction models'. Further, though the WHO categorizations of chronic diseases encompass approximately 80% of presently prevalent chronic diseases, not all diseases are captured within the categories of cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases. To ameliorate this potential limitation, the search strategy was completed in consultation with a research librarian to help ensure its comprehensiveness. The existence of a MeSH term for the concept of risk prediction models would enable a more directed, comprehensive search within this field, allowing for the identification of a greater number of studies.

The outcomes examined in this systematic review may also present some concerns, specifically the outcome of patient behaviour. Though it has been characterized in existing studies through behaviours or actions such as smoking cessation or changes in physical activity, one possible area that should be emphasized that exists on the pathway from medication prescription to health outcome is medication accessibility and subsequent medication adherence. For example, antihypertensive medications may reduce a patient's risk of stroke by almost 40% through reductions in in systolic and diastolic blood pressure (by 10-12 mmHg and 5-6 mmHg, respectively).[235] These decreases are possible only if patients are taking the medications as prescribed. Measures of medication accessibility and adherence would provide a strong measure of patient

behaviour, but also provide some explanation for any changes or lack thereof for patient health outcomes.

This review may also have been prone to some biases. The risk of bias summary (Figure 11) indicates that this study may have been prone to biases in terms of confounding and external validity, and was potentially statistically underpowered. This study may also have been susceptible to publication bias. Publication bias occurs in a systematic review when studies that fulfill the eligibility criteria are not identified because they have not been published, resulting in a biased perspective of the literature.[190,236] Further, an assessment of publication bias was not possible as there were an insufficient number of studies to conduct a formal assessments as per the Cochrane Handbook.[190] Other biases may have been introduced during the conduct of the meta-analyses as well. For example, though 10 studies reported the impact of model use on systolic blood pressure, only 4 were included in the meta-analysis, which could introduce bias if these 4 studies are not representative of the entire evidence base.[236] Though measures to reduce the risk of biases were enacted, such as grey literature searches and having multiple reviewers, the potential for bias still exists.

Variations in terms of study conduct may pose as issues of heterogeneity. For example, nearly half of all studies in this review provided lifestyle advice in addition to the patient's absolute risk of developing disease. Additional studies also provided referrals to other healthcare providers, and in some cases, provided multiple training opportunities to physicians regarding model use and intent. Because of these additional intervention components, it becomes difficult to discern with certainty to what extent the effect is a result of model use. Risk presentation also varied between studies, with some studies providing absolute risk in paper format, with others communicating risk verbally or through use of a computer- or tablet-based platform. Further, in some studies, relative measures of risk were provided in addition to the absolute measures, potentially influencing both the physician and patient response to risk. Differences in length of follow-up may also account for variations in changes in risk factor levels. Indeed, Price et al. followed their patients for one month, while the period of follow-up for Jiao et al. (2015) was three years. The combination of these two studies, hypothetically, indicates

that the magnitude of effect remains constant across the period of follow-up, a potentially unfair assumption. Given the sparsity of model impact studies, all identified studies that met the eligibility criteria were included. As the field develops, however, additional criteria may be applied to future systematic reviews to reduce the risks associated with study heterogeneity.

7.7 Implications for future research and practice

This systematic review and meta-analysis was most limited by the heterogeneity of studies. Inspection of the I^2 values for the meta-analyses indicates the analyses and thus the variation across studies was due to heterogeneity, not chance. To strengthen the body of literature, there is a strong need for consistent, overarching guidance of the appropriate conduct for impact analysis studies. The Cochrane Collaboration Prognosis Reviews Methods Group was formed to evaluate the growing body of literature pertaining to prediction models, and the group developed the CHARMS checklist, a critical appraisal and data extraction checklist for systematic reviews of prediction models.[60] However, the checklist only accounts for development and validation studies, with little to no applicability to impact analysis studies given the difference in aims, study designs, and reporting.[60]

A tool guiding the conduct of impact analysis studies would ensure the methodological rigour of studies and strengthen the body of evidence exploring the impact of risk prediction models. The present body of literature indicates several inconsistencies that should be addressed. Firstly, a significant amount of heterogeneity in study design exists, with existing studies ranging from pre-post observational studies to cluster randomized trials, which, while not necessarily precluding the possibility of, reduces the comparability between studies. Interventions are also uniquely presented across studies, such as providing lifestyle advice additional to the model-derived risk. Pertaining to study conduct, periods of follow-up are non-uniform, ranging from a period of weeks to years, both reducing the comparability of studies as well as possibly not allowing for changes in behaviour or health outcomes. The reporting of impact studies is also inconsistent, with diversity in measurement and presentation of study outcomes. The development of such a tool could help inform the conceptualization, conduct, analyses,

and reporting associated with impact analysis studies, creating greater consistency in the literature, and allowing for the meaningful interpretation of study findings.

Future studies should also examine the implementation of risk prediction models in primary care settings. The use of risk prediction models in clinical practice faces several barriers, including those of time and uncertainty. The physician-patient interaction is already temporally restricted, reducing the amount of time available for preventive services.[153] Further, models exist for several health outcomes, and each model is designed for a specific target population. As such, there exists uncertainty about which models are appropriate for a physician's patients.[70] This problem may be compounded by the rising prevalence in multimorbidity, which would necessitate multiple models being used for a single patient, significantly increasing the time spent in preventive services. In recognition of these time constraints, uncertainty, and the rise in multimorbidity globally, there exists the need to streamline the process. This may be accomplished through the incorporation of models in routine electronic medical records allowing for automated calculation of absolute risk, or the creation of models capable of predicting for multiple health outcomes (multimorbidity risk prediction models). By streamlining this process, the process of implementing risk prediction models in clinical practice may be eased.

7.8 Conclusion

This systematic review and meta-analysis brought to light the inconsistencies in the conduct of impact analysis studies, and inconsistencies in general within the growing field of prediction modelling. This study identified a small group of studies that examined the impact of prediction models on clinical and behavioural outcomes. Though these studies may have been affected by methodological discrepancies and the review would be strengthened by a unified method for conducting model impact studies, they do provide some measure of support for the use of prediction models in primary care settings, and indicate that future research must be undertaken to ascertain the most effective methods of implementing these tools in clinical practice.

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Appendix A: The Gusto-I Model predicting risk of mortality at 30 days for patients who experience myocardial infarction.

Probability of death within 30 days = 1 / [1 + exp(-L)], where L is given by:

L= 3.812 + 0.07624*age - 0.03976*minimum(SBP, 120) + 2.0796[Killip class II] + 3.6232[Killip class III] + 4.0392[Killip class IV] - 0.02113*heart rate + 0.03936(heart rate-50) - 0.5355[inferior MI] - 0.2598[other MI location] + 0.4115[previous MI] - 0.03972*height + 0.0001835(height-154.9) + 3 - 0.0008975(height-165.1) + 3 + 0.001587(height - 172.0) + 3-0.001068(height-177.3) + 3 + 0.0001943 (height-185.4) + 3 + 0.09299 (time to treatment)-0.2190[current smoker]-0.2129[former smoker] + 0.2497[diabetes] - 0.007379*weight + 0.3524[previous CABG] + 0.2142[SK and intravenous heparin] + 0.1968[treatment with SK and subcutaneous heparin] + 0.1399[combination TPA and SK plus IV heparin] + 0.1645[hx of hypertension] + 0.3412 [hx of cerebrovascular disease] - 0.02124 age*[Killip class II] - 0.03494 age*[Killip class III] - 0.03216 age · [Killip class IV]

Appendix B: Search strategies and citations retrieved

Embase

Step	Search Terms	Results
1	Risk/ or Patient Risk/ or Expectancy/ or Risk Factor/	1792018
2	limit 1 to (human and english language and yr="1976 -Current")	1455591
3	((Risk adj3 (adjust* or factor*)) or Probabilit* or Likelihood).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	1416454
4	limit 3 to (human and english language and yr="1976 -Current")	1091256
5	1 or 3	2225620
6	2 or 4	1740409
7	Cardiometabolic Risk/ or Cardiovascular Risk/ or Coronary Risk/ or Reynolds risk score/ or Framingham risk score/ or CHADS2 Score/ or PROCAM Score/ or QRISK Score/ or Receiver Operating Characteristic/ or exp Area Under the Curve/ or exp "prediction and forecasting"/ or survival prediction/ or survival rate/ or exp decision support system/ or clinical decision making/ or medical decision making/	1720383
8	limit 7 to (human and english language and yr="1976 -Current")	1289143
9	("Risk scor*" or risk tool* or risk estimat* or risk assess* or risk function* or risk equation* or risk calc* or risk scor* or risk predict* or risk factor calc* or risk chart* or risk engine* or risk appraisal* or prediction model* or risk algorithm* or scoring* method* or scoring scheme* or roc curve or area under curve or AUC or c-statistic* or C index* or C indices*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	586636
10	limit 9 to (human and english language and yr="1976 -Current")	477129
11	7 or 9	2100566
12	8 or 10	1590351
13	Chronic Disease/ or Cardiovascular Disease/ or Heart Disease/ or Vascular Disease/ or Lung Disease/ or Chronic Lung Disease/ or Chronic Obstructive Lung Disease/ or Asthma/ or Diabetes Mellitus/ or Insulin Dependent Diabetes Mellitus/ or Non Insulin Dependent Diabetes Mellitus/ or exp Neoplasm/	5711682
14	limit 13 to (human and english language and yr="1976 -Current")	3678673
15	(Chronic disease* or Chronic illness* or chronically ill or non-communicable disease* or cardiovascular disease* or vascular disease* or heart disease* or stroke or respiratory disease* or asthma or COPD or chronic obstructive pulmonary disease* or diabetes or diabetes mellitus or diabetic or cancer* or neoplasm* or metastatic* or metastisi* or metastases or carcinoma* or tumo?r*).mp. [mp=title,	6617097

	abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	
16	limit 15 to (human and english language and yr="1976 -Current")	4218997
17	13 or 15	7255289
18	14 or 16	4569682
19	exp Primary Health Care/ or General Practice/	221104
20	limit 19 to (human and english language and yr="1976 -Current")	159278
21	(Primary health care or primary care or primary healthcare or primary medical care or family practice or family medicine or general practi*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	330910
22	limit 21 to (human and english language and yr="1976 -Current")	232874
23	19 or 21	330910
24	20 or 22	232874
25	5 and 11 and 17 and 23	8318
26	6 and 12 and 18 and 24	7311

Medline

Steps	Search terms	Results
1	Risk/ or Risk Factors/ or Risk Adjustment/	782446
2	limit 1 to (english language and humans and yr="1976 -Current")	669642
3	((Risk adj3 (adjust* or factor*)) or Probabilit* or Likelihood).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1202769
4	limit 3 to (english language and humans and yr="1976 -Current")	903884
5	1 or 3	1290060
6	2 or 4	973836
7	Algorithms/ or Probability/ or Bayes Theorem/ or Likelihood Functions/ or Proportional Hazards Models/ or "Sensitivity and Specificity"/ or ROC Curve/ or exp Decision Support Techniques/ or Area Under Curve/ or Clinical Decision-Making/ or exp Risk Assessment/	900317
8	limit 7 to (english language and humans and yr="1976 -Current")	661515
9	("Risk scor*" or risk tool* or risk estimat* or risk assess* or risk function* or risk equation* or risk calc* or risk scor* or risk predict* or risk factor calc* or risk chart* or risk engine* or risk appraisal* or prediction model* or risk algorithm* or scoring* method* or scoring scheme* or roc curve or area under curve or AUC or c-statistic* or C index* or C indices*).mp. [mp=title, abstract, original title, name of substance word, subject heading	375007

	word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
10	limit 9 to (english language and humans and yr="1976 -Current")	300610
11	7 or 9	989961
12	8 or 10	712702
13	Chronic Disease/ or Cardiovascular Diseases/ or exp Heart Diseases/ or exp Vascular Diseases/ or exp Lung Diseases, Obstructive/ or Diabetes Mellitus/ or Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or Neoplasms/ or exp Neoplasms by Histologic Type/ or exp Neoplasms by Site/	5281905
14	limit 13 to (english language and humans and yr="1976 -Current")	3414820
15	(Chronic disease* or Chronic illness* or chronically ill or non-communicable disease* or cardiovascular disease* or vascular disease* or heart disease* or stroke or respiratory disease* or asthma or COPD or chronic obstructive pulmonary disease* or diabetes or diabetes mellitus or diabetic or cancer* or neoplasm* or metastatic* or metastisi* or metastases or carcinoma* or tumo?r*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4887214
16	limit 15 to (english language and humans and yr="1976 -Current")	3031693
17	13 or 15	6516965
18	14 or 16	3962675
19	Primary Health Care/ or Comprehensive Health Care/ or exp General Practice/	133832
20	limit 19 to (english language and humans and yr="1976 -Current")	92993
21	(Primary health care or primary care or primary healthcare or primary medical care or family practice or family medicine or general practi*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	231332
22	limit 21 to (english language and humans and yr="1976 -Current")	1588565
23	19 or 21	236748
24	20 or 22	160459
25	5 and 11 and 17 and 23	2696
26	6 and 12 and 18 and 24	2396

CINAHL

Step	Search Terms and options	Results

1	(MH “Risk Factors+”) OR (MH “Health Screening+”) OR (MH “Patient Assessment+”) Search modes - Boolean/Phrase	176674
2	(MH “Risk Factors+”) OR (MH “Health Screening+”) OR (MH “Patient Assessment+”) Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	85634
3	Risk adj3 (adjust* OR factor*) OR Probabilit* OR Likelihood Search modes - Boolean/Phrase	36531
4	Risk adj3 (adjust* OR factor*) OR Probabilit* OR Likelihood Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	27669
5	1 or 3	109548
6	2 or 4	208539
7	(MH "Predictive Value of Tests") OR (MH “Predictive Research”) OR (MH “Models, Statistical”) OR (MH “Decision Support Techniques+”) OR (MH “Decision Making, Clinical”) OR (MH “Clinical Assessment Tools”) OR (MH “Risk Assessment”) OR (MH “ROC Curve”) OR (MH “Survival Analysis+”) Search modes - Boolean/Phrase	201806
8	(MH "Predictive Value of Tests") OR (MH “Predictive Research”) OR (MH “Models, Statistical”) OR (MH “Decision Support Techniques+”) OR (MH “Decision Making, Clinical”) OR (MH “Clinical Assessment Tools”) OR (MH “Risk Assessment”) OR (MH “ROC Curve”) OR (MH “Survival Analysis+”) Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	146268
9	“Risk scor*” OR risk tool* OR risk estimat* OR risk assess* OR risk function* OR risk equation* OR risk calc* OR risk scor* OR risk predict* OR risk factor calc* OR risk chart* OR risk engine* OR risk appraisal* OR prediction model* OR risk algorithm* OR scoring* method* OR scoring scheme* OR roc curve OR area under curve OR AUC OR c-statistic* OR C index* OR C indices* Search modes - Boolean/Phrase	90777
10	“Risk scor*” OR risk tool* OR risk estimat* OR risk assess* OR risk function* OR risk equation* OR risk calc* OR risk scor* OR risk predict* OR risk factor calc* OR risk chart* OR risk engine* OR risk appraisal* OR prediction model* OR risk algorithm* OR	56570

	scoring* method* OR scoring scheme* OR roc curve OR area under curve OR AUC OR c-statistic* OR C index* OR C indices* Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	
11	7 or 9	235929
12	8 or 10	167860
13	(MH “Chronic Disease”) OR (MH “Cardiovascular Diseases”) OR (MH “Heart Diseases”) OR (MH “Vascular Diseases”) OR (MH “Lung Diseases”) OR (MH “Lung Diseases, Obstructive+”) OR (MH “Diabetes Mellitus”) OR (MH “Diabetes Mellitus, Type 1”) OR (MH “Diabetes Mellitus, Type 2”) OR (MH “Neoplasms”) OR (MH “Neoplasms by Site+”) OR (MH “Neoplasms by Histologic Type+”) Search modes - Boolean/Phrase	359492
14	(MH “Chronic Disease”) OR (MH “Cardiovascular Diseases”) OR (MH “Heart Diseases”) OR (MH “Vascular Diseases”) OR (MH “Lung Diseases”) OR (MH “Lung Diseases, Obstructive+”) OR (MH “Diabetes Mellitus”) OR (MH “Diabetes Mellitus, Type 1”) OR (MH “Diabetes Mellitus, Type 2”) OR (MH “Neoplasms”) OR (MH “Neoplasms by Site+”) OR (MH “Neoplasms by Histologic Type+”) Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	129339
15	Chronic disease* OR Chronic illness* OR chronically ill OR non-communicable disease* OR cardiovascular disease* OR vascular disease* OR heart disease* OR stroke OR respiratory disease* OR asthma OR COPD OR chronic obstructive pulmonary disease* OR diabetes OR diabetes mellitus OR diabetic OR cancer* OR neoplasm* OR metastatic* OR metastisi* OR metastases OR carcinoma* OR tumo?r* Search modes - Boolean/Phrase	521893
16	Chronic disease* OR Chronic illness* OR chronically ill OR non-communicable disease* OR cardiovascular disease* OR vascular disease* OR heart disease* OR stroke OR respiratory disease* OR asthma OR COPD OR chronic obstructive pulmonary disease* OR diabetes OR diabetes mellitus OR diabetic OR cancer* OR neoplasm* OR metastatic* OR metastisi* OR metastases OR carcinoma* OR tumo?r* Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	194062
17	13 or 15	200021
18	14 or 16	39265
19	(MH “Primary Health Care”) OR (MH “Family Centered Care+”)	39265

	Search modes - Boolean/Phrase	
20	(MH “Primary Health Care”) OR (MH “Family Centered Care+”) Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	13019
21	Primary health care OR primary care OR primary healthcare OR primary medical care OR family practice OR family medicine OR general practi* Search modes - Boolean/Phrase	78566
22	Primary health care OR primary care OR primary healthcare OR primary medical care OR family practice OR family medicine OR general practi* Limiters - Published Date: 19760101-20170331; English Language; Human Search modes - Boolean/Phrase	32297
23	19 or 21	83275
24	20 or 22	33712
25	5 and 11 and 17 and 23	857
26	6 and 12 and 18 and 24	555

Appendix C: Study eligibility criteria

Title/abstract level

Inclusion criteria:
- Intervention is or includes a risk prediction model
- The model is prognostic
- The model generates a predicted risk for a chronic disease
- The study must test the effect of the intervention (i.e. model impact)
- Include articles with no age, geographic, or sex restrictions

Exclusion criteria:
- Model is diagnostic
- Model assesses for behavioural, mental, or acute health outcomes (i.e. risk of STI infection, risk of schizophrenia, risk of fracture)
- Patients are generally symptomatic for the outcome of the model (>20%)
- The study does not occur in a primary care setting
- The healthcare professional is not a physician
- The citation is for an editorial or opinion piece
- The study describes only the development or validation of risk prediction models

Full-text level

- Confirmation of criteria from title/abstract level of screening

Inclusion criteria:
- The study assesses the effect of the intervention on physicians and/or patients
- Include studies with a control group

Exclusion criteria:
- The study does not include some form of a control group (i.e. no pre- data in a pre-post study)
- Exclude studies that only evaluate economic impact of model use

Appendix D: Brief description of interventions administered

Author, year	Description of intervention
van den Brekel-Dijkstra et al., 2016[201]	Patients completed web-based questionnaire. Those identified at increased risk based on personal information (e.g. sociodemographic, personal health) completed biometric and laboratory testing, generating 10-year CVD risk. Patients receive health plan containing: 1) outcome of risk assessment (normal, moderately elevated risk, seriously elevated risk), 2) explanation of health risk and benefits of preventive action, 3) individual opportunities for lifestyle change, and 4) links to local providers of lifestyle interventions. Follow-up electronic questionnaire sent six months after receiving tailored advice.
Usher-Smith et al., 2015[219]	Patients informed of change in NICE guidelines (change in statin prescription threshold from 20% absolute risk to 10%), provided information leaflet regarding recommendations, risk calculation, statins, and lifestyle advice. Leaflet encourages lifestyle modifications and invited to visit clinics to discuss statins. At clinic appointment, patients told QRISK score, discuss statins, and offered opportunity for further review in the future if hesitant. Data were retrieved from practice electronic records.
Sorensen et al., 2011[220]	Patients underwent medical history interview regarding previous disease, and tobacco and medication use. Risk factors were measured and CVD risk was calculated. Participants and their general physicians received written reports. If at elevated risk, participants were notified to contact their physician. Follow-up questionnaires were mailed to patients six months following screening examination.
Bach-Nielsen et al., 2005[199]	A previous study recruited participants, who were randomly allocated to either a control group, where lifestyle questions were asked, or an intervention group, where a health screening, including calculation and written provision of cardiovascular risk, was conducted. The subject of the present article was a qualitative study, where patients were interviewed regarding their participation in screening, their experiences and findings, assessments of their own health, views regarding health promotion and screening, and opinions on consultations with their physician.
Chang et al., 2016[203]	Data were extracted for patients registered at a practice participating in the Clinical Practice Research Datalink. Patients were categorized as either Health Check attendees and nonattendees. Patients during the Health Check received their cardiovascular risk as well as tailored management strategies including lifestyle advice.
Cochrane et al., 2012[204]	Patients from 38 general practices were recruited, and practices were randomized to the NHS Health Check group or the NHS Health Check plus additional lifestyle support group. The NHS Health Check included usual general care, such as smoking cessation or medication services and provision of

	risk score. Lifestyle support included consultation with lifestyle coaches, the development of health improvement plans, and lifestyle priorities with referrals to free support sessions for weight management, physical activity, dietary support, and positive thinking. One year follow-up measures were obtained.
Vagholkar et al., 2014[221]	Randomization occurred at the level of the practice. Physicians were trained (3-hour workshop) in the use of the New Zealand CV risk calculator and recommendations for cardiovascular risk based on Australian and New Zealand guidelines. Intervention patients received 20-30 minute consultations where risk was calculated, and were provided appropriate management based on risk levels and current guidelines. Control patients received a general health check. Physicians reassessed cardiovascular risk at the 12-month health check.
Grover et al., 2008[209]	Patients were stratified by risk level (very high, high, or moderate) and randomized to receive either printed, individualized risk profiles or usual care. Risk profiles display probability of coronary disease risk over an 8-year period as well as cardiovascular age, a life expectancy adjusted for risk of coronary disease and stroke based on average life expectancy of Canadians of the same age and sex. Risk profiles were mailed to physicians prior to the next patient visit, and shown to intervention patients at their visit as well as provided to patients to take home. Biometric measures (blood pressure, lipids) were taken 2-4 weeks prior to and at each follow-up visit. Updated risk profiles were discussed with intervention patients at each visit.
Courtney et al., 2015[205]	Patients who received PreDx results were identified from a comprehensive electronic medical database in the Dallas-Fort Worth area. A comparison group matched for age, sex, selected diagnoses (similar to intervention group), and metabolic risk factors was also selected from the same database. A report was provided to patients including the PreDx results, a numerical score distinguishing risk of type 2 diabetes, as well as the individual patient's risk compared to the general population, and the levels of the patient's individual biomarkers with their normal ranges. Data were also collected regarding intensity of care, risk factor monitoring, and prescription medication.
Engberg et al., 2002[206]	Patients randomly selected from one district in Denmark, and received a questionnaire about general demographic information and lifestyle, as well as questions about psychosocial status and psychosocial life events. Patients randomly allocated to 1 of 3 groups: 1) questionnaire (includes healthy lifestyle pamphlet) only, 2) questionnaire and health screening, and 3) questionnaire, health screening, and follow-up health discussions. Health screenings provided each patient with an estimate of cardiovascular risk. If at elevated risk, patients received feedback relating to lifestyle changes, and were encouraged to see their general practitioner. Health discussions were 45 minute consultations with general physicians, where patient concerns were addressed and lifestyle goals were established. Health discussion groups were offered annual consultations; all other groups had follow-ups at 1 and 5 years post-baseline.

Ford et al., 2001[207]	The Clinical Biochemistry laboratory database at Birmingham Heartlands Hospital was searched for all CHD risk requests made in 1998. Physicians made requests by providing a laboratory request form with a blood sample, the cardiovascular risk is calculated. Researchers visited practices to review patient case notes for those a risk request was made for. Risk results were confirmed, as well as reasons why tests were ordered, prescribed drugs both before and after the risk request, and any other management changes.
Grover et al., 2007[208]	Physicians attended a regional investigator meeting, which included training on interpreting risk profiles, national lipid guidelines, and the study protocol. Patients were screened with a complete medical evaluation. Patients were randomized to usual care or ongoing feedback regarding calculated coronary risk. Risk profiles including 10-year coronary risk were discussed with patients by study physicians in the intervention arm, while usual care patients did not receive risk profiles. Risk profiles were computer printouts with disease risk as well as cardiovascular age, and contained relative risks as well as absolute risk. Patients were followed for one year with biometric measures taken before and during each follow-up visit (3 month intervals).
Jiao et al., 2015[211]	Patients (in the RAMP-DM group) of public general outpatient clinics underwent risk factor screening for diabetes-related complications and were stratified according to JADE classification (high, medium, low risk). RAMP-DM subjects received appropriate interventions and education according to risk. Usual care patients were managed by physicians without risk assessment and stratification.
Jiao et al., 2014[210]	Patients (in the RAMP-DM group) entering the program underwent risk factor assessment and potential existing diabetic complications upon enrolment, and were stratified as low, medium, or high risk. Different management strategies were provided to them, such as consultation with allied health professionals. Patients under usual care were managed solely by physicians without risk assessment and stratification.
Law et al., 2014[212]	Physicians prospectively collected data amongst ambulatory patients. Physicians determined patient cardiovascular risk, and reported subsequent treatment decisions.
Lowensteyn et al., 1998[213]	Community-based family physicians were invited for participation, and assigned a study site. Study sites were allocated to the profile group or the control group. Physicians then invited patients. Physicians inputted risk factor data, then patient completed a questionnaire outlining attitudes and knowledge of CVD as well as current lifestyle and medical problems. Profile patients received a printed copy of their risk profile. Patients were scheduled for a follow-up visit 3 to 6 months later. New risk factor data were collected at

	follow-up. Profiles provide 8-year coronary risk, and risk reductions for modifications of risk factors.
Mehta et al., 2014[214]	Patients recruited upon their physician's use of PREDICT, a web-based clinical decision program that generates an absolute risk for patients. Patients were stratified according to cardiovascular risk (high, moderate, or low risk). PREDICT database was linked to the Pharmaceutical Collections to collect data on dispensing of medications.
Palmieri et al., 2011[215]	Physicians were trained in the USE of the 10-CR score, and downloaded the CUORE.EXE software, which allows users to calculate CVD risk based on patient characteristics. It also provides a hypothetical risk based on modifications of risk factors to favourable levels, and present risk reductions for behaviour changes. Information is printed along with lifestyle recommendations, and presented to patients, and sent to a central database. Updated information on risk factor levels, absolute risk, prescribed therapies and lifestyle recommendations were sent to the same database. Cardiovascular events were recorded during follow-up.
Powers et al., 2011[216]	Patients who agreed to participate received a baseline survey, and patients were randomized to either a standard risk factor education group or a personalized risk communication group. Standard education included written patient education materials covering established risk factors and how factors can be improved. Personalized risk communication patients received the standard education as well as information based on their personal CHD and stroke risk scores, both verbally and graphically. The average and optimal scores were published alongside their personal risk. Patients were provided with strategies to improve their risk (risk factor modification and lifestyle factors). Data were collected from medical records and interviews.
Price et al., 2011[217]	Participants were recruited from four general practices in Oxfordshire, and were randomized to either the risk factor group or personalized risk group. Risk factor group patients received their blood pressure, total cholesterol and fasting glucose values and were told if they were elevated. Personalized risk group patients received their cardiovascular disease risk estimate. In a 2 x 2 factorial design, patients were also randomized to receive or not receive lifestyle advice. The personalized risk information displayed current risk and achievable risk, a hypothetical risk if all targets for risk factors are obtained.
Romero et al., 2008[218]	Medical records of patients from the Internal Medicine Clinic at the Naval Medical Center San Diego were reviewed to identify eligible patients. Baseline data were recorded. A poster including the Framingham Risk Score was placed in examination rooms of the clinic, and physicians were encouraged through semi-regular announcements to improve guideline adherence. Outpatient medical records of another patient sample were reviewed and data were recorded.

Volpe et al., 2007[222]	General physicians recruited patients with a diagnosis of hypertension. Patient blood pressure levels and estimated stroke risk was measured at both the initial visit and during the follow-up visit. Risk factor data were recorded directly in a computerized scoring algorithm. No recommendations were made to physicians regarding therapeutic interventions.
Wind et al., 2015[223]	Study sponsors recruited general physicians, who then recruited 10 consecutive patients. Data were collected from the patients' medical records. At baseline, physicians estimated patient 10-year CHD risk based on their own subjective judgement, and then using the UKPDS risk engine. Study sponsors trained physicians on how to use the risk engine, interpret CHD risk, and determine whether differences between subjectively calculated risk and UKPDS derived risk warranted medication adjustment. Data on risk estimates, risk factor levels, and medication adjustments were recorded.
Bellows et al., 2014[200]	Physicians at two clinics in Hawaii were selected. IndiGO guidelines were implemented using automatic data extraction for all adult patients, which automatically calculated risk scores. Physicians selected patients, who were shown videos explaining the guidelines. Physicians and patients then used IndiGO in a shared decision-making session with a printed summary displaying all chosen interventions, and predicted risks of heart attack and stroke if interventions are implemented. Propensity score matching was used to identify a control group of patients receiving usual care.
Burgess et al., 2011[202]	The Aboriginal and Torres Strait Islander Adult Health Check (AHC) was implemented in remote communities. During the AHC, cardiovascular risk was assessed identifying patients with elevated CVD risk, and other behavioural risk factor values were collected via questionnaire. The AHC also consisted of chronic disease care planning, with patient education and intervention delivery, treatment goals are negotiated with patients, and follow-up monitoring and care planning. Patients were followed for three years at six month intervals.

Appendix E: Comparison of baseline and follow-up measures as per Chang et al. (2015).[203]

Risk factor	Group	Before intervention	After intervention
QRISK2, % 10-year risk	Intervention	6.7±5.9	6.2±5.3
	Control	5.1±5.3	4.9±5.0
Systolic blood pressure, mmHg	Intervention _	131.9±17.4	130.0±12.7
	Control	128.5±13.6	129.3±11.3
Diastolic blood pressure, mmHg	Intervention	80.2±10.5	78.5±7.7
	Control	78.7±8.2	78.7±6.7
Body mass index (kg/m^2)	Intervention	27.7±5.1	27.7±5.0
	Control	26.9±4.1	27.2±4.0
Total cholesterol, mmol/L	Intervention	5.5±1.0	5.3±0.8
	Control	5.3±0.6	5.3±0.6
Smoking prevalence, % of group	Intervention	17.9	16.3
	Control	22.2	20.8
Statin prescribed, % of group	Intervention	9.7	15.3
	Control	3.1	4.3
Antihypertensive prescribed, % of group	Intervention	4.8	9.9
	Control	1.8	4.4

Values are presented as mean ± standard deviation, where available.

Appendix F: Comparison of baseline and follow-up measures as per Cochrane et al. (2012)[204]

Risk factor	Group	Baseline	Follow-up
CVD risk (%)	Health Check	32.9±9.7	29.4±9.7
	Health Check Plus	31.9±10.0	29.2±10.1
Systolic blood pressure, mmHg	Health Check	146.0±17.0	138.3±14.7
	Health Check Plus	144.4±16.2	138.7±14.6
Diastolic blood pressure, mmHg	Health Check	84.9±9.5	80.5±8.8
	Health Check Plus	85.3±9.6	81.5±8.9
Total cholesterol (mmol/L)	Health Check	5.7±0.9	5.0±1.0
	Health Check Plus	5.7±0.9	5.1±1.0
Total cholesterol/HDL cholesterol, mmol/L	Health Check	4.8±1.0	4.2±1.1
	Health Check Plus	4.9±1.1	4.4±1.1
Weight (kg)	Health Check	82.6±13.8	82.8±13.5
	Health Check Plus	85.0±14.5	84.3±14.5
Body mass index (kg/m^2)	Health Check	27.5±4.1	27.6±4.1
	Health Check Plus	28.7±5.0	28.4±4.9
Waist circumference (cm)	Health Check	99.5±11.8	97.9±10.7
	Health Check Plus	101.3±11.2	99.1±11.4

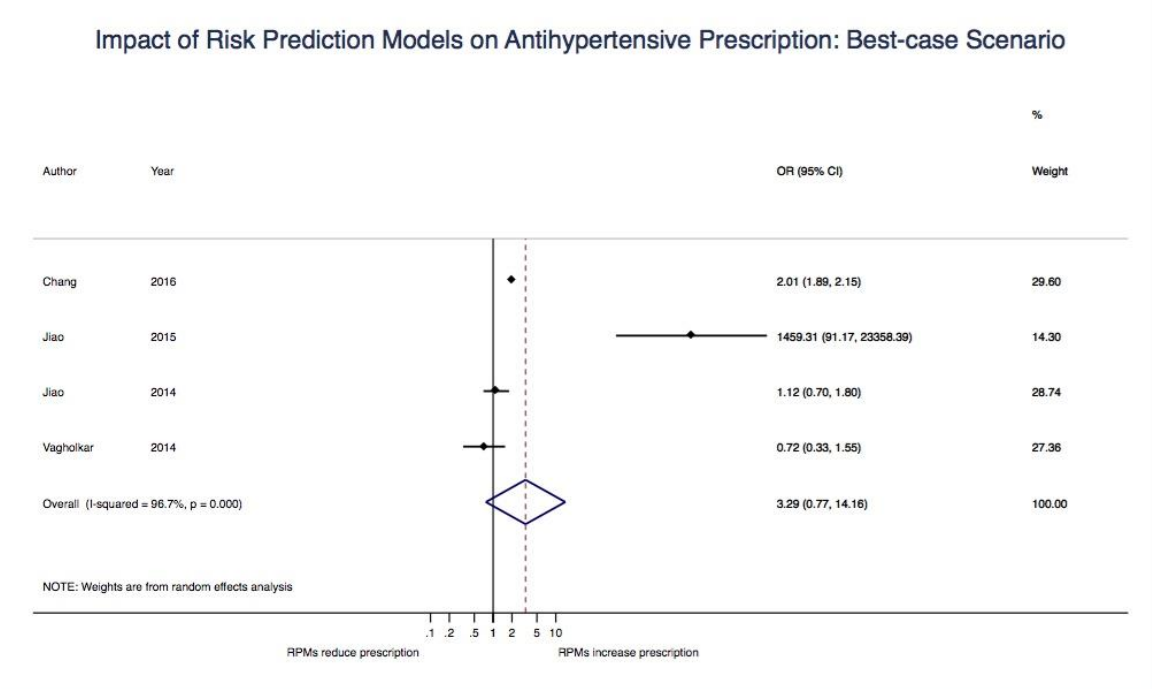
Values are presented as mean ± standard deviation.

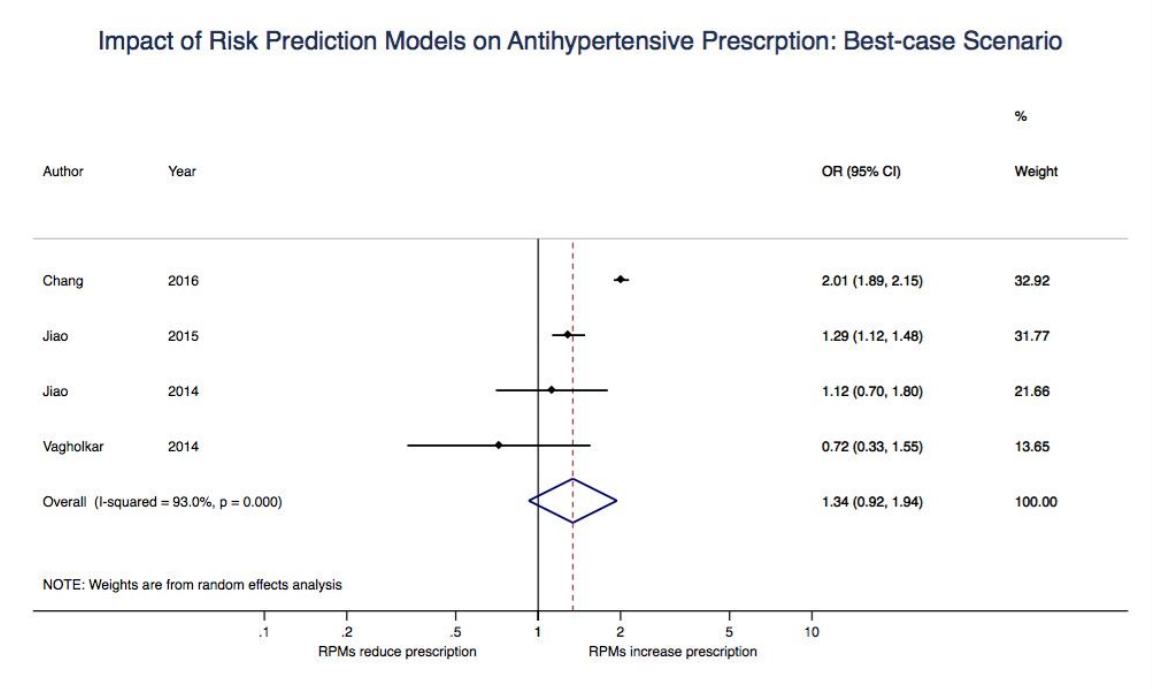
Appendix G: Comparison of baseline and follow-up measures for Jiao et al. (2015)[211]

Risk factor	Group	Before intervention	After intervention
BMI (kg/m^2)	Intervention	25.33±3.74	25.07±3.79
	Control	25.33±3.90	25.11±3.92
Systolic blood pressure, mmHg	Intervention	135.41±17.05	130.12±14.68
	Control	135.45±16.56	132.35±15.51
Diastolic blood pressure, mmHg	Intervention	75.11±10.34	71.60±10.26
	Control	75.08±9.77	73.23±9.72
HbA1c (%)	Intervention	7.24±1.23	7.13±1.09
	Control	7.24±1.24	7.25±1.26
Total cholesterol, mmol/L	Intervention	5.08±0.94	4.43±0.82
	Control	5.08±0.95	4.49±0.86
HDL-C (mmol/L)	Intervention	1.22±0.32	1.28±0.34
	Control	1.22±0.32	1.31±0.35
LDL-C (mmol/L)	Intervention	3.13±0.82	2.51±0.69
	Control	3.14±0.83	2.55±0.72
Triglyceride (mmol/L)	Intervention	1.64±1.10	1.43±0.87
	Control	1.64±1.05	1.43±0.97
Current smoker	Intervention	927 (10.2)	346 (9.0)
	Control	906 (10.0)	235 (8.6)
On glucose-lowering drugs	Intervention	7943 (87.3)	7999 (90.0)
	Control	7929 (87.2)	7143 (83.6)
On antihypertensive drugs	Intervention	6637 (73.0)	7112 (80.0)
	Control	6673 (73.4)	6493 (76.0)
On lipid-lowering drugs	Intervention	1189 (13.1)	4551 (51.2)
	Control	1225 (13.5)	3903 (45.7)
On insulin	Intervention	105 (1.2)	534 (6.0)
	Control	130 (1.4)	386 (4.5)

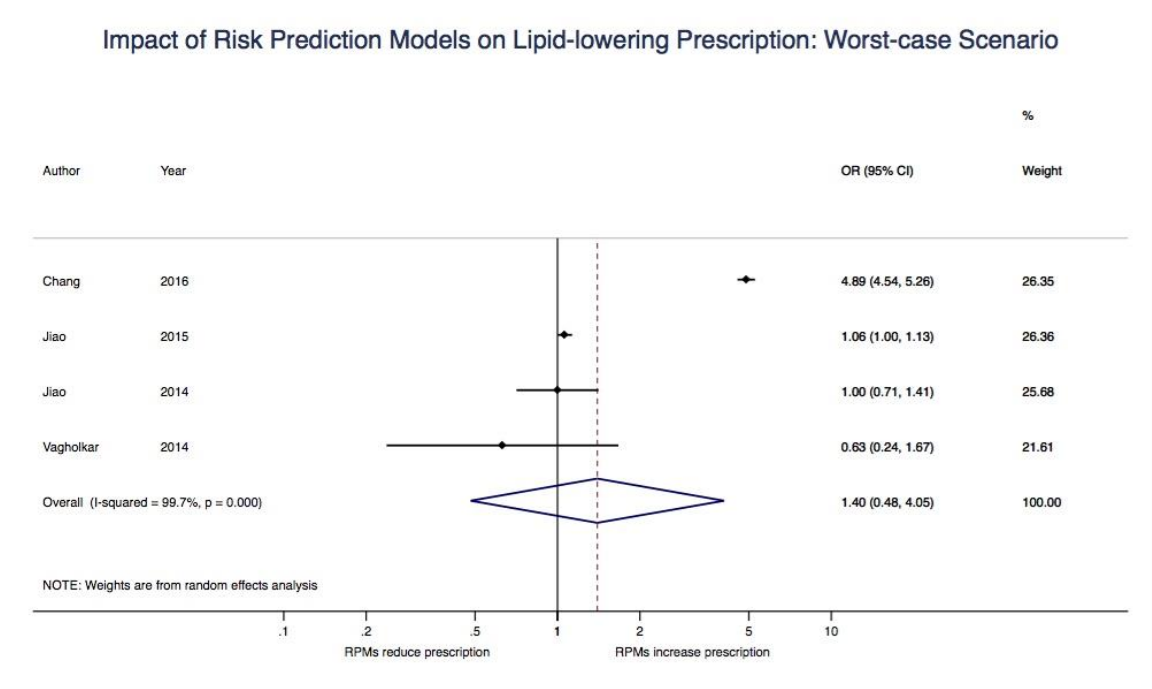
Values are presented as mean ± standard deviation or *n* (%).

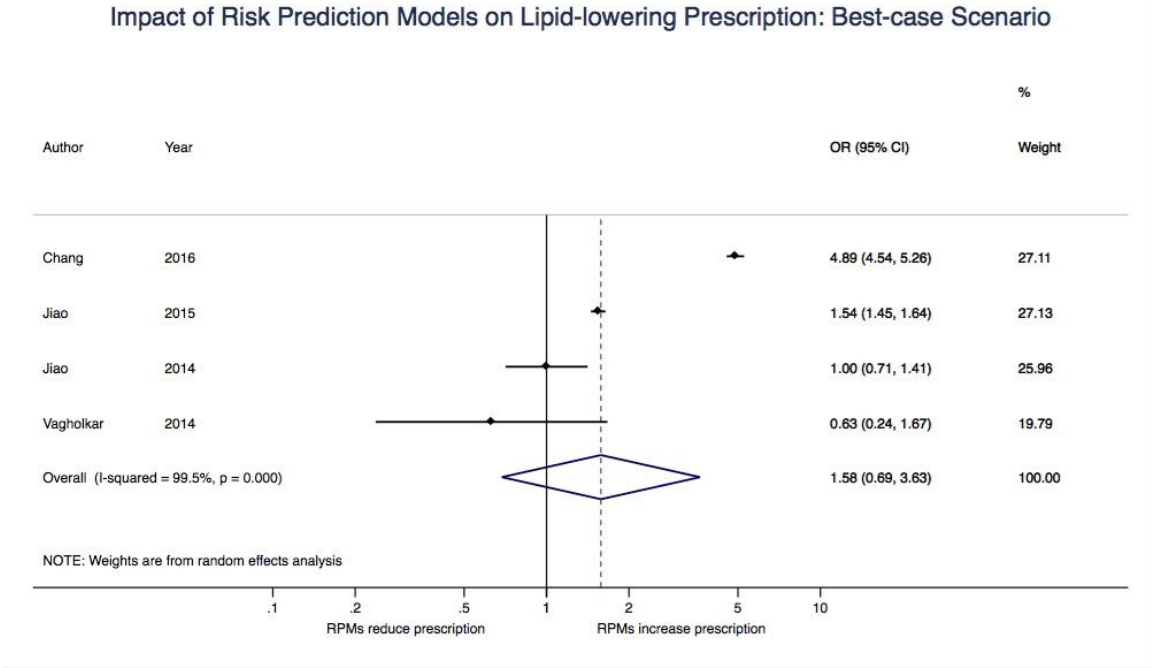
Appendix H: Forest plots for best- and worst-case scenarios (antihypertensive medication prescription)



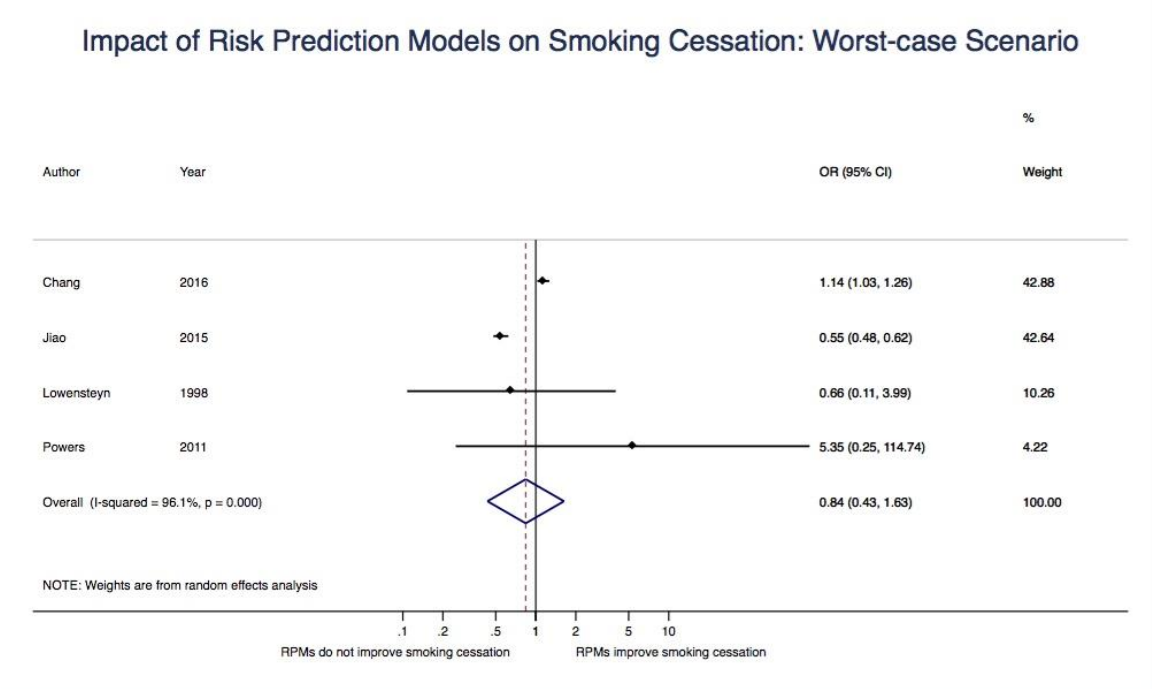


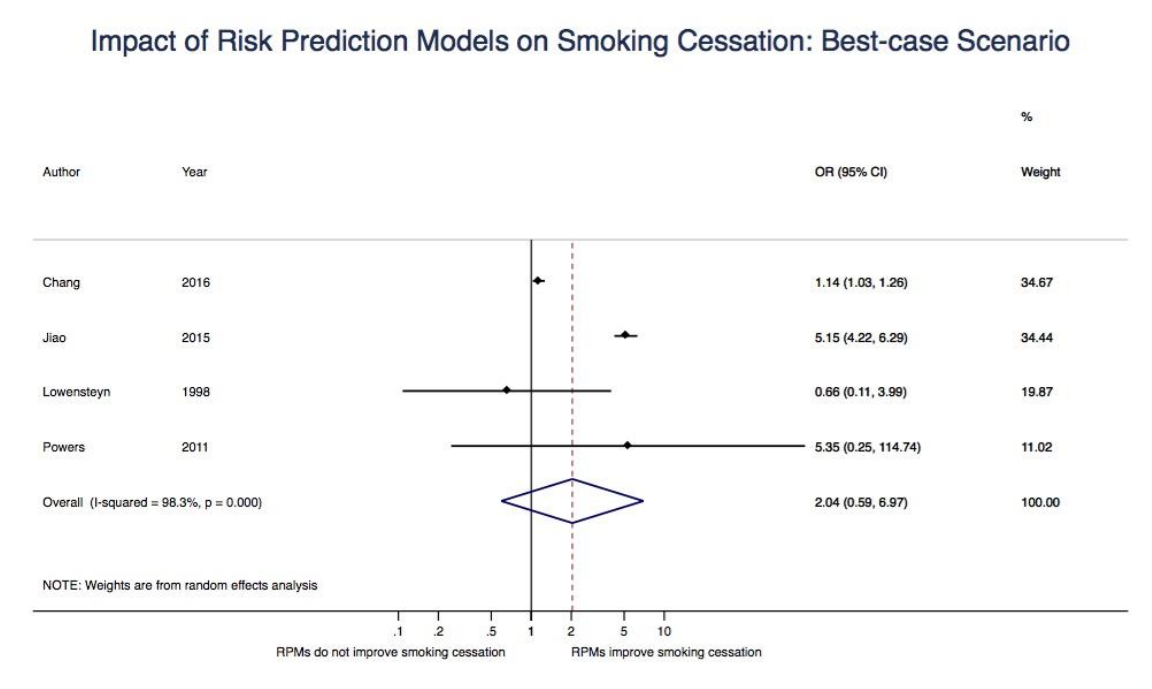
Appendix I: Forest plots for best- and worst-case scenarios (lipid-lowering medication prescription)





Appendix J: Forest plots for best- and worst-case scenarios (smoking cessation)





Curriculum Vitae

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June 2015
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