Title: A scoping review of the predictive models of diabetes complications

AUTHORS

Ruth Ndjaboue, PhD (Corresponding author)
VITAM Research Centre for Sustainable Health
2525, chemin de la Canardière
Entrée A-1-2, 3e étage, bureau A-3421
Québec (Québec) G1J 0A4
418 821-9481

Vice-décanat à la recherche et au développement professionnel continu
Faculté de Médecine, Université Laval
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Tel : 418 656 2131 (#2963)
Email: Ruth.ndjaboue@fmed.ulaval.ca

Gérard Ngueta, PhD
Département de médecine sociale et préventive
Faculté de Médecine, Université Laval
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Email:Gerard.Ngueta.1@ulaval.ca

Charlotte Rochefort-Brihay, **MD Cand.**
Faculté de Médecine, Université Laval
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Email: charlotte.rochefort-brihay.1@ulaval.ca

Sasha Delorme, Patient
Diabetes Action Canada
Regina, Saskatwewan, Canada
Email: fersher18@hotmail.com

Daniel Guay, Patient
Diabetes Action Canada
Montreal, Quebec, Canada
Email: danielguay57@videotron.ca

Noah M. Ivers, MD, PhD
Women's College Hospital
Family Practice Health Centre
77 Grenville Street
M5S 1B3
Toronto, Ontario, Canada
Email: Noah.Ivers@wchospital.ca

Baiju R. Shah, MD, PhD
Sunnybrook Health Sciences Centre
2075 Bayview Ave., Room G106
M4N 3M5
Toronto, Ontario, Canada
Email: baiju.shah@ices.on.ca

Sharon Straus, MD, PhD
Department of medicine
University of Toronto
27 King's College Circle
M5S 1A1
Toronto, Ontario, Canada
Email: sharon.straus@utoronto.ca

Catherine H. Yu, MD, MHSc
Division of Endocrinology & Metabolism,
St. Michael's Hospital,
30 Bond St,
M5B 1W8
Toronto, Ontario, Canada
Email: yuca@smh.ca

Sandrine Comeau, B.Sc. Cand.
Vice-décanat à la pédagogie et au développement professionnel continu
Faculté de Médecine, Université Laval
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Email: sandrine.comeau.1@ulaval.ca

Imen Farhat, MSc, PhD cand.
Department of Epidemiology, Biostatistics and Occupational Health
Faculty of Medicine, McGill University
1020 Pine Avenue West
H3A 1A2
Montreal, Quebec, Canada
Email: imen.farhat@mail.mcgill.ca

Charles Racine, B.A cand.
Vice-décanat à la pédagogie et au développement professionnel continu
Faculté de Médecine
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Email: charles.racine.2@ulaval.ca

Olivia Drescher, MSc.
Diabetes Action Canada
Faculté de Médecine, Université Laval
1050, Avenue de la médecine
G1V A06
Quebec City, Quebec, Canada
Email: Olivia.drescher@fmed.ulaval.ca

Holly O. Witteman, PhD
Department of Family and Emergency Medicine
Faculty of Medicine, Université Laval
1050, Avenue de la médecine
Quebec City, Quebec, Canada
G1V 0A6
VITAM Research Centre for Sustainable Health
2525, chemin de la Canardière
Entrée A-1-2, 3e étage, bureau A-3421
Québec (Québec) G1J 0A4
418 821-9481
Email: Holly.witteman@fmed.ulaval.ca

ABSTRACT (337 words)

Background: Diabetes often places a large burden on people with diabetes, their families, health systems, and societies. Some of this burden is attributable to the complications of diabetes. However, evidence from models predicting the risk of diabetes complications in people with diabetes (called patients) remains unclear. Guided by patient partners living with diabetes, this review aimed to identify and describe existing prediction models of physical and mental health complications of diabetes.

Methods: Building on existing frameworks, we systematically searched for studies in Ovid-Medline and Embase. We included studies describing prognostic prediction models that used data from patients with prediabetes or any type of diabetes published between 2000 and April 2020, regardless of country or publication language. Two or more independent reviewers screened articles and extracted data using a standard methodology. We narratively synthesized findings using established reporting standards.

Results: We included 78 studies reporting 260 risk prediction models of cardiovascular complications (n=42 studies), mortality (n=16), kidney complications (n=14), eye complications (n=10), hypoglycemia (n=8), nerve complications (n=3), cancer (n=2), fracture (n=2) and dementia (n=1). Prevalent and patient-important complications were poorly (e.g., amputation) or not (e.g., mental health) represented. Most studies analysed data from people with type 2 diabetes (n=54), aged 30 years or older (n=76), and of diverse race/ethnicity (n=40). Few studies analysed data from people with type 1 diabetes (n=8) or younger people (18 to 30 years old)(n=1). Potential and candidate predictors vary according to the diabetes complications. Studies with statistical details of calibration and discrimination mostly exhibited good model performance.

Conclusion: Although selected prediction models of diabetes complications concern a broad range of health conditions, the predicted risk of complications remains unclear for social minority groups, teenagers, and people with type 1 diabetes. By offering a comprehensive, systematic, rigorous knowledge synthesis, our review may serve to support shared-decision making about preventive strategies for diabetes complications. Future studies should address as yet unmet needs for analyses of certain complications and patient groups, and should consistently assess and report external validation and all relevant statistics of models' performance.

Scoping review registration: https://osf.io/fjubt/

Key words: diabetes, review, risk prediction, predictive models, complication, patient

BACKGROUND

Diabetes is a non-communicable disease affecting 693 million people, with 1.6 million deaths are directly attributed to diabetes each year worldwide.[1] According to World Health Organization reports, both the number of cases and the prevalence of prediabetes and diabetes have been steadily increasing over the past two decades.[1] The burden of diabetes on individuals and health care systems is primarily related to other diabetes-related health conditions people develop after living with diabetes for a period of time (hereafter called "complications").[1,2]

Early identification of people with diabetes at increased risk of complications is an important priority for clinicians.[3] Risk prediction models have become increasingly popular in clinical research to support and inform medical decision-making.[4] In the context of diabetes, models predicting the risk of complications are useful to identify people at higher risk of complications in order to inform decision making regarding preventive actions or treatments to avoid or delay complications.[5]

Prediction models of other conditions in people with diabetes often compare people with and without diabetes, which is of limited relevance for people already living with diabetes.[6–8] Previous systematic reviews of prediction models of complications mostly assessed cardiovascular and coronary diseases,[9,10] and little is known about microvascular and psychological conditions.[5,11] This scoping review aimed to identify and synthesize existing prediction models of physical and mental complications in people with any type of diabetes mellitus or prediabetes (hereafter called "patients").

Methods/Design

This knowledge synthesis used a well-established Scoping Review framework,[12,13] the Preferred Reporting Items in Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) for reporting (refer to Appendix A-3).[14] Our published protocol[15] provides details of the methods that we describe succinctly in this paper.

Patient and Public involvement

Our patient-oriented approach ensures that we capture diabetes complications that are relevant to people living with diabetes.[16] Our research team includes diverse experts, including people with diabetes.[15] We recruited eight people with diabetes from a patient-oriented network and we involved them in every step of this review[17] in order to better integrate what matters to them in risk communication (Table 3).[18] Three authors (DG, SD, HOW) live with diabetes.

ELIGIBILITY CRITERIA

We included studies that met all our eligibility criteria, as stated in the protocol.[15] Specifically, the **population** was restricted to people of any age with prediabetes and any type of diabetes,[19] except gestational diabetes. We did not include data mixing people with and without diabetes, unless there were separate sub-analyses for individuals with diabetes

only. Models based on the Framingham Risk Score were excluded because it was originally derived from people without diabetes.[20] We included data collected at the individual level but not the group level, and we exclude studies that did not involve real persons (e.g., simulation studies).[21]

The **concept** refers to clinically diagnosed and self-reported complications, which the World Health Organization defined as serious damage to the heart, blood vessels, eyes, kidneys or nerves as a consequence of diabetes.[1] We also considered mortality and other chronic diseases that matter to patient partners, especially diabetes-related mental health.[15] We exclusively included studies that focused on the onset and not the progression of complications. We did not include studies about social or economic consequences of diabetes because they are likely to be highly dependent on social and environmental factors and less modifiable at the individual level.[15]

Concerning the **context**, we restricted this review to studies published from 2000 because both diabetes treatment and modeling approaches have greatly improved in the last two decades. We only included cohort studies in which the measurement of predictors preceded that of outcomes.[22] We included studies with quantitative data for at least one prediction prognostic model estimating the risk of onset of one or multiple diabetes complications and for which there was reported evidence of internal or external validation or both.[23,24] Because diabetes risk complications are often evaluated in epidemiological studies, we additionally explored potential biases in original studies. Previous work using a similar approach suggested that it may help readers make informed use of findings[25] and alleviate the potential challenge of evaluating reliability and consistency in data of diverse nature.[26]

SEARCH STRATEGY AND DATA SELECTION

As mentioned in our protocol,[15] the search strategy aligned with previous work and what matters to patient partners. In 2018, we retrieved references from electronic databases, previous papers, and experts' consultation. We used EndNote[27] and Covidence,[28] two management software packages, for data storage and screening. As planned,[15] two people among the team members (RN, CRB, CF, IF, JC, SC, JM, YY) independently screened titles, abstracts and full text articles to determine eligibility after a calibration exercise. In case of many disagreements, a third reviewer (RN, GN, CRB, TP, SC, CR) repeated the screening and discussed all remaining disagreements in meetings with all reviewers. In April and July 2020, we updated this search strategy using the same methodology. [15]

DATA COLLECTION AND EXTRACTION

Given the lack of validated checklists for data extraction in scoping reviews on risk prediction models, we used criteria of a well-known checklist for systematic reviews[29] which aligns with the scoping review methodology[13] to guide our data extraction process. We (RN, IF, TP, CRB) developed, pre-tested and used an extraction grid (Excel spreadsheet) with specific criteria for data extraction (Appendix A-1 and A-2), including all important statistical and epidemiological aspects of selected studies and models (e.g., number of models, derivation and/or validation features, follow-up time, participants' characteristics,

predictors, outcomes, main limitations). Four people (CRB, CR, SC, TP) independently completed the data extraction and resolved all discrepancies through discussion. Two epidemiologists (RN, GN) reviewed and extracted complex data and approved selected studies. Reasons for exclusion are available in Appendix A-8.

Although not mandatory for scoping reviews,[30] we took advantage of the new Prediction model Risk Of Bias Assessment Tool (PROBAST)[31] to appraise the quality of included studies as stated in our protocol.[15] Two experts with doctorates in Epidemiology (RN, GN) rated studies based on the quality of participants' selection and follow-up, predictors and outcomes assessment, sample size and statistical analyses based on the information available in the published papers (Appendix A-3).[23,24,32] We paid attention to the retention rate during follow-up as it may influence the model accuracy or generalization to other people with diabetes. We did not assess general representativeness in this context because people with diabetes are not necessarily representative of the general population. Based on their epidemiological strength, studies were deemed to be of high, moderate or low quality. Data quality assessment informed our data synthesis and interpretation.

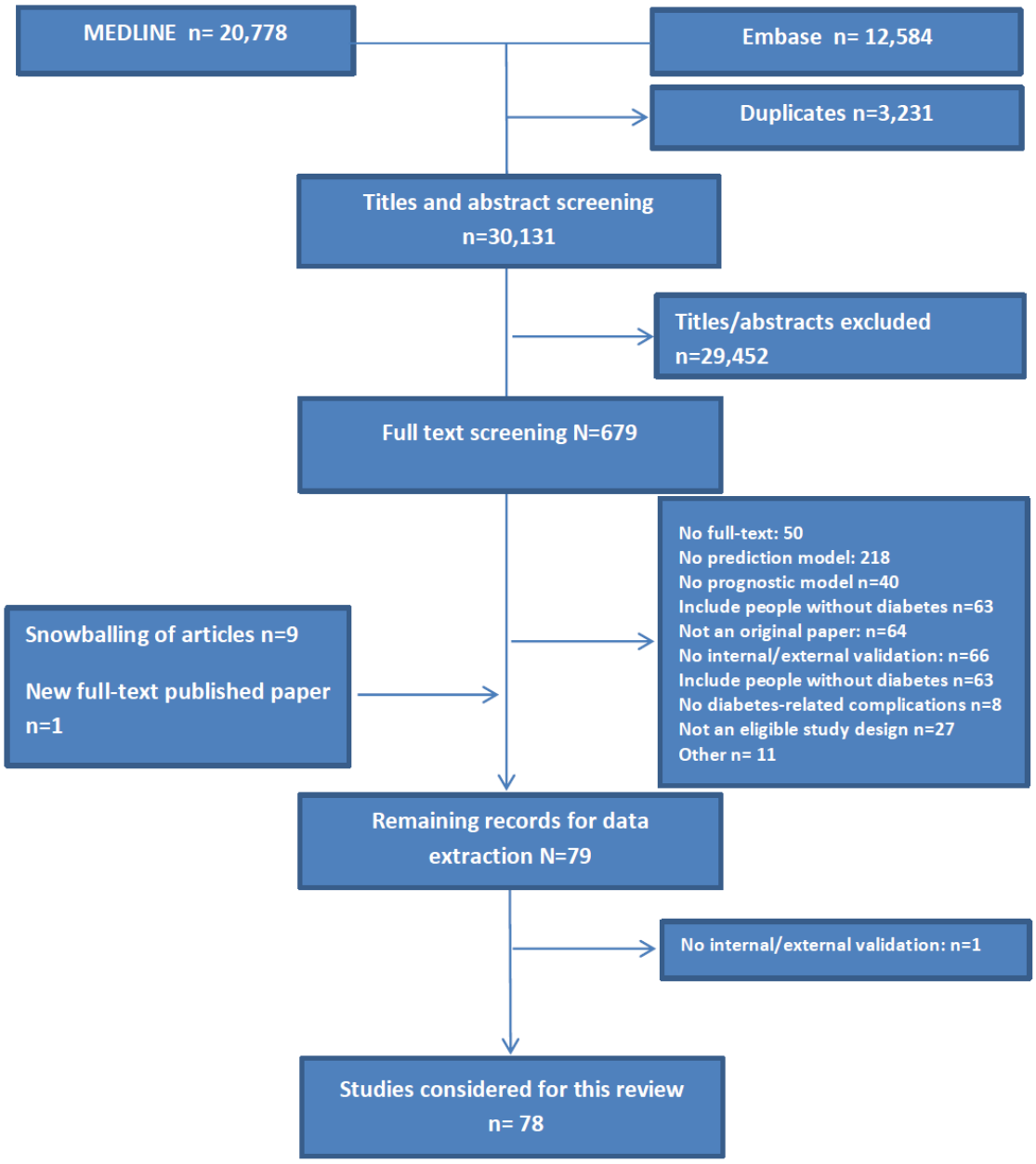
DATA ANALYSIS AND SYNTHESIS

We performed a descriptive and narrative synthesis of studies and resulting prediction models in our extraction file using a deductive approach.[13,33] We attempted to resume heterogeneous data models' performance, especially the calibration and the discrimination. The model calibration, which represents the gap between what is predicted and what is observed,[34] was tested in diverse ways (e.g., Life-table method, Hosmer Lemeshow test, Predicted/Observed ratio, calibration slope, Greenwood-D'Agostino-Nam). The smaller the gap, the better the calibration. The discrimination capacity or model fit, which refer to how good a model is able to predict the occurence of the outcome in a similar or different population, is tested during the internal validation and external validation. Discrimination tests are often concerned with the overall discrimination capacity using AUC metric or c-statistics which range between 0 and 1, with greater values indicating better model performance.[35] For this review, we included AUC > 0.7 as being good. We also paid attention to missing information that may have been relevant to this work while exploring potential explanations for quantitative data inconsistencies.

RESULTS

From the 30,131 unique references retrieved from electronic databases and ten manually searched references (snowballing of articles (n=9) and published full-paper of conference abstracts (n=1)), we identified a total of 78 studies reporting 260 unique models (see Fig. 1 and appendix A-7 and A-8).

Figure 1. Flow chart for included articles in this scoping review.



Studies and models description

Publication years ranged from 2001 to 2020, with the majority of included articles (n = 69; 73%) published since 2015 (Figure 2). Of the 246 models that reported their final set of predictors, there was a median of 10 predictors included in the final models (range: 2 to 388). Predictors include demographics (e.g., age, sex), health conditions or disease history (e.g., infection), clinical characteristics (e.g., Body Mass Index (BMI)), medication (e.g., insulin, statin), lab tests (e.g., cholesterol, A1c) and/or lifestyle-related factors (e.g., smoking, physical activity) (Table 1). Most models included sex or gender as candidate predictors

(n=61) and 3 performed sex-specific analyses.[36–39] Finally, approximately 57% of the studies included external validation models (n=45). A detailed list of population characteristics can be found in Appendix A-4.

Selected studies were either restricted to people with type 1 (n=8)[39–46] or type 2 diabetes (n=54),[35–38,47–96] or combined both types (n=7).[97–103] Some studies did not specify diabetes types (n=8)[104–111] and one mixed people with prediabetes and diabetes (n=1).[112]

Most selected studies included adults only, either up to 60 years old (n=11)[39,40,42,44–46,64,82,96,98,99] or without an upper age limit (n=65).[35–38,43,47–54,56–63,65–81,83–95,97,100–112] One study was restricted to people aged 18 years old or younger at baseline (n=1)[41] and one did not report participants' age (n=1).[55]

Most studies included people of diverse race/ethnicity (n=40).[35,39,47,48,51,52,57–59,62–64,67,69,70,73,76,79–88,93,95–97,100–105,108–110] A small number of studies studied only either white people (n=2),[54,56] Black people (n=1)[48] or Asian people (n=9).[36–38,68,74,75,89–91] A moderate number of studies (n=26) did not report participants' race/ethnicity.[40–46,49,50,53,55,60,61,65,66,71,72,77,78,94,98,99,106,107,111,112]

All included studies studied male and female participants.

We sorted findings from included studies by complications, which led to ten categories. All-cause mortality and outcomes including heterogeneous health conditions are presented separately. Figure 3 presents the number of models by outcomes and by diabetes type. Also refer to Appendix A-5 and A-6

Cardiovascular complications

We included 42 studies reporting 116 validated prediction models.[36,39,40,43,44,47–51,53,60,63–65,70–73,75–78,80–82,84,86,88–90,92–94,96,100,105,108–110] The most common outcomes predicted in these models were: fatal and non-fatal coronary heart diseases/myocardial infarction/heart failure (n=43/116), fatal and non-fatal cerebrovascular disease and stroke (n=10/116), revascularization surgery (n=1), and other unspecified or combined fatal and non-fatal cardiovascular conditions (n=63/116). Of these models, 6 focused on deaths from cardiovascular conditions. Based on clinician experts' (SS, BS, CY) recommendations, we included one study[70] involving people with both diabetes and heart failure at baseline given that the outcome (atherosclerotic disease) was a complication that is independent from heart failure.[114] Fewer models predicted the risk of cardiovascular conditions in people with type 1[39,40,43,44] compared to type 2 diabetes.[36,47–51,53,60,63–65,70–73,75–82,84,86,88–90,92–94,96,110] Of the studies that reported their final set of predictors, the most selected predictors were: age (n=70/105), biomarkers (e.g., cholesterol, urine creatinine) (n=83/105), hemoglobin A1C (n=72/105), smoking (n=85/105), blood pressure (n=87/105) and sex (n=59/105). Of the models that had detailed information regarding the statistical performance, prediction times varied from 1 to 10 years depending on the model, some studies reported good calibration in the internal (n=27/74) and external (n=45/73) validation or exhibited good discrimation capacity in the internal (n=37/67) and external validation (n=29/59).

All cause-mortality

We included 16 studies reporting on 40 validated prediction models.[37,47–49,54,56,67,72,85,87,92,95,106,109] Models predicted deaths from all-cause (n=31/40) and mortality from non-cardiovascular (n=1/40), non vascular (n=5/40), neoplasm (n=1/40), respiratory (n=1/40) and genitourinary (n=1/40) diseases. Two models predicted the combined risk of all-cause and CVD deaths.[48] Studies focusing on a single specific death cause and mortality that was modeled with health conditions are listed elsewhere. Most of the models on mortality (n=39/40) studied only people with type 2 diabetes,[37,45,47–49,54,56,67,72,79,85,87,88,92,95,106] and none studied only those with type 1 diabetes. All studies reported their final set of predictors. The most selected predictors were: age (n=34/40), diabetes-related medication (e.g., insulin, metformin) (n=34/40), biomarkers (e.g., cholesterol, urine creatinine) (n=33/40), BMI (n=26/40), sex (n=25/40), other existing or past chronic conditions (e.g., hypoglycemia, lung disease, heart failure, retinopathy) (n=21/40) and hemoglobin A1c (n=19/40). Of the models that had detailed information regarding the statistical performance, prediction times varied from 1 to 10 years, models were mostly well calibrated in the internal (n=21/27) and external (n=12/23) validation, and also exhibited good discrimination capacity in the internal (n=18/21) and external (n=15/19) validation.

Kidney complications

We included 14 studies reporting in 41 validated prediction models.[38,46–48,57,58,68,69,72,74,79,83,88] Often, models predicted microalbuminuria, macroalbuminuria, renal failure or end-stage renal disease, and doubling of serum creatinine (n=21/41). Some models predicted end-stage renal disease (ESRD) (n=11/41), albuminuria (n=5/41), renal function decline (n=1/41) or kidney failure/chronic renal failure (3/41). Except for three models from the same study[46] predicting the risk of kidney conditions in type 1 diabetes, all models predicted outcomes only for people with type 2 diabetes. Of the studies that reported their final set of predictors, the most selected predictors were: hemoglobin A1c (n=30/41) and other biomarkers (e.g., creatinine, eGFR) (n=38/41), age (n=23/41), blood pressure (n=23/41), sex (n=21/41), diabetes-related medication (ex: statin, metformin, hypertensive, anticoagulants, etc.) (n= 22/41), other chronic conditions (n=19/41) and smoking status (n=24/41, including current smokers n=12). Of the models that had detailed information regarding the statistical performance, prediction times varied from 3 to 10 years, models were mostly well calibrated in the internal (n=10/14) and external (n=13/13) validation, and also exhibited good discrimination capacity in the internal (n=17/28) and external (n=18/24) validation.

Eye complications

We included 10 studies reporting on 20 validated prediction models.[41,42,47,48,55,72,88,97–99] The most common eye conditions predicted in those models were: retinopathy (n=18/20), eyes edema or macular edema (n=1/20) and blindness (n=1/20). Most models on eye conditions studied people with type 2 diabetes (n=14/20), type 1 diabetes (n=2/20), or combined both types (n=4/20). Of the studies that reported their final set of predictors, the most selected predictors were: hemoglobin A1c (n=18/20), biomarkers (e.g., cholesterol, serum creatinine)

(n=12/20), blood pressure (n=12/20) and BMI-related factors (n=11/20). Of the models that had detailed information regarding the statistical performance, prediction times varied from 6 months to 10 years, models were mostly well calibrated in the internal (n=6/6) and external (n=6/6) validation but few exhibited good discrimation capacity in the internal (n=5/12) and external (n=2/6) validation.

Hypoglycemia

Concerning We included 8 studies reporting on 14 validated prediction models.[35,52,61,62,101,103,104,107] Some of the selected models focused on severe hypoglycemia (n=4/14), which refers to an episode with typical symptoms (e.g., sweating, dizziness, tremor, visual disturbance) that resolves after treatment (oral carbohydrate, intramuscular glucagon, or intravenous glucose) administered by another person.[115] Models often predicted the risk of hypoglycemia in people with type 2 diabetes[35,52,61,62] or unspecified types. None of these models focused on type 1 diabetes. The number of predictors in final models varied greatly. One model had 388 selected predictors, including 13 demographic variables, 89 diagnosis variables, 180 pharmacy variables, 68 procedure variables, 30 laboratory variables and 8 utilization variables.[35] Of the thirteen models that detailed their final set of predictors, the most selected predictors were: age (n=13/13), insulin use (n=13/13), diabetes-related medication other than insulin (n=13/13), other chronic conditions (e.g., renal disease, retinopathy, cardiovascular conditions, cancer, dementia, depression) (n=13/13), prior hypoglycemic episode (n=9/13), biomarkers (e.g., creatinine, eGFR) (n=8/13), hemoglobin A1c (n=8/13), BMI or waist circumference (n=7/13) and race/ethnicity (n=7/13). Of the models that had detailed information regarding the statistical performance, prediction times varied from 6 months to 5 years, models were well calibrated in the internal (n=2/2) and external (n=1/1) validation, and most models exhibited a good discrimation capacity in the internal (n=12/12) and external validation (n=6/7).

Nerve complications

We included 3 studies reporting in 8 validated prediction models.[48,55,88] Diabetic peripheral neuropathy (DPN), the most common cause of neuropathy in people with diabetes[116] was specifically assessed in one study.[88] The two other studies assessed diverse neuropathy conditions, including pressure sensation loss, ankle jerk loss, vibratory sensation loss.[48,55] All models studied only people with type 2 diabetes. The number of predictors in the final model varied from 4 to 12, and the most selected predictors were: hemoglobin A1c (n=8/8), sex (n=5/8), race/ethnicity (n=5/8), other chronic condition (n=5/8), biomarkers (e.g., cholesterol) (n=5/8), blood pressure (n=4/8), age (n=4/8) and diabetes related medication other than insulin (n=4/8). Prediction times varied from 3 to 10 years. One study reported good calibration of its models in internal (n=4/4) and external validation (n=1/1).[48] Detailed information of the model performance the internal validation showed a good discrimination capacity in some cases (n=3/8). The single model validated externally had an acceptable discrimination capacity.[48]

Cancer

We included 2 studies reporting in 2 validated prediction models. These models predicted the 3-year risk of pancreatic cancer[111] and the 5-year risk of all cancer,[91] in people with unspecified diabetes and type 2 diabetes respectively. No study was restricted to people with type 1 diabetes. The number of predictors in the final model varied from 4 to 11 and the most selected predictors were: age (n=2/2), biomarkers (e.g., total cholesterol) (n=2/2), other chronic conditions (n=2/2), smoking (n=2/2) and hemoglobin A1c (n=1/2). Both models had good calibration and good discrimation capacity in internal validation. None of those studies reported external validation.

Fracture

We included a single study reporting 2 validated prediction models. These models predicted the 5-year risk of hip fracture or major fracture in people newly diagnosed with type 2 diabetes.[66] The final set of predictors include: age (n=2/2), sex (n=2/2), previous major fracture (n=2/2), previous ischemic heart disease (n=2/2), nutritional supplements (n=2/2) and diabetes related medication (n=1/2). Both models exhibited good calibration and good discrimation capacity in the internal validation. None of those studies reported external validation.

Cognitive complications

We included a single study with one validated model predicting the 10-year risk of dementia in people with type 2 diabetes.[59] The final set of predictors include: age, sex, education, microvascular disease, diabetic foot, macrovascular disease, acute metabolic event and depression. This model exhibited a good calibration and discrimation capacity in external validation. No internal validation was reported in the study.

Concerning other complications, we included 5 studies in 16 validated models predicting the risk of diverse health conditions in people with diabetes, including macro and microvascular complications (n=1),[102] infectious diseases (n=1),[102] metabolic diseases (n=1),[102] at least one of five major outcomes (amputation, blindness, CHD/stroke, end-stage renal failure/dialysis, death) (n=4),[45] and cardiovascular diseases and non-cardiovascular mortality (n=4),[49] and diabetes-related hospitalization (n=5).[35,84]

Validated models predicting the 7- and 8-year risk of the first of five major outcomes in people with type 1 diabetes exhibited good discrimination capacity in the internal and external validation, but did not consistently reached good calibration.[45] The four final sets of predictors included: age, waist-height ratio, hemoglobin A1c, albumin/creatinine ratio and cholesterol.

Validated models predicting the 10-year risk of cardiovascular diseases or non-cardiovascular mortality in people with type 2 diabetes exhibited good calibration in the internal validation but not in the external validation. The single model with discrimination capacity information

was acceptable.[49] The four final sets of predictors included sex, smoking, blood pressure, BMI, biomarkers, duration of diabetes, insulin and history of cardiovascular diseases.

Validated models predicting the 1-, 3-, 5- and 8-year risk of hospitalization in people with type 2 diabetes all exhibited a good calibration and discrimination capacity in the internal validation. The final set of predictors in the single study that provided such details was: age, gender, duration of diabetes, BMI, hospitalization status one year prior to baseline, biomarkers, diabetes-related medications and other chronic conditions.[85]

DISCUSSION

This review aimed to identify and synthesize prognostic prediction models of complications in people diagnosed with diabetes. Our findings suggest that modifiable and non-modifiable factors work together to predict the risk of cardiovascular complications, mortality, kidney complications, eye complications, nerve complications, hypoglycemia, fracture and dementia.

Comparing research focus to patients' priorities

Throughout this project and in prior work,[18] discussions with patient partners suggested that people with diabetes are primarily concerned about complications that would negatively and irreversibly impact length of life[117] or lifestyle,[118,119] such as amputation, blindness, or stroke. People with diabetes are also concerned about temporary and reversible complications (e.g., fracture) that may affect well-being and social function.[118]

There was some inconsistency between the research focus on diabetes complications and the prevalence or the burden of these complications. On one hand, cardiovascular conditions were the most common predicted conditions in this review and also represent the most commonly-reported conditions in people with diabetes.[5] On the other hand, only 7% of included models concerned eye conditions even though these are one of the most frequent diabetic complications in people with diabetes and are associated with other diabetes complications and mortality.[120,121] Additionally, despite patient partners' strong interest in preventing foot ulcerations or lower extremity amputation, prediction models about these complications were scarce. No validated prognostic prediction models of foot ulcer or amputation were included in this review although they represent a frequent cause of hospitalization and one of the most common, severe and costly complications of diabetes mellitus,[122] and also lead to major socio-economic consequences for the patients. In yet another mismatch, despite the well-known association between diabetes and mental health issues[123] and patient partners' expressed interests, we found no prediction model on this topic. For epidemiologists to do better in responding well to the challenges most often faced by people with diabetes, we recommend that future prediction models address patients' priorities.

In addition to failing to address conditions of interest to people living with diabetes, the included models rarely answered questions regarding subpopulations. Patient partners (including caregivers of children with diabetes) expressed particular interest in questions related to length of diabetes in children and race/ethnicity. Concerning length of diabetes,

although clinical symptoms of complications are uncommon in childhood and adolescence,[124] people diagnosed with diabetes in childhood may experience complications in teenage or young adulthood.[125] However, very limited models used data from young adults and teenagers and some studies [68,84,85] even excluded patients under 30 years old, which greatly limits how our findings may apply to younger people. The fact that the risk of diabetes complications often increases with diabetes duration and most models include length of diabetes among candidate predictors of most selected models may not be sufficient to capture what may be happening in young patients.[126] An accurate prediction of diabetes complication risks in teenagers might be helpful to inform what is happening in adulthood and to inform how patients' and caregivers' concerns may change over time/throughout life stages. Furthermore, the majority of prediction models addressed race/ethnicity poorly. Even in countries with high proportions of people who are Black, Indigenous, South Asian, or otherwise racialized (e.g., Australia, USA), almost all models were constructed on pooled data and offered no subanalyses for racial/ethnic subgroups. We further discuss racial and ethnic inequities and their implications below.

Comparing research focus to clinical information needs

Knowing more about the perspectives and needs of those concerned with diabetes can potentially improve information supply and health outcomes.[127] According to Biernatzki 2018, deep insight into the perspectives of people with diabetes is urgently needed to provide needs-driven information.[128] For this reason, we involved patient partners (including caregivers) and clinicians throughout this study, from defining objectives to drafting this manuscript, and we will involve them in the dissemination of findings. We sought to synthesize relevant information in an accessible and practical way while taking into consideration diverse clinical information needs.

It is recommended that clinicians communicate with people having diabetes about their risk of complications[129] prior to any treatment or recommendation in order to address patients' clinical information needs. Our findings may support clinician-patient communication, particularly regarding the course of diabetes. Information about the 'course of disease' is the second highest of nine patient information needs, especially information about the 'consequences of diabetes' on physical health, lifestyle and social life.[128] This review can also help address patient information needs related to 'diabetes through the life cycle', 'prevention' and 'research'.[128] Moreover, our findings can address the needs of other stakeholders of diabetes care, such as caregivers who may look for synthesized, evidence-based and easily readable information as they are working together with patients to minimize or mitigate the burden of diabetes and its complications.[130,131]

How might this be used for patients and clinicians

Patients are often unable to accurately estimate their personal risk of complications.[132,133] Our evidence-based and specific findings can help inform patients and minimize the fear based on lack of knowledge that has been found to affect diabetes complication risks.[129] Although providing a list of candidate and selected predictors is not a requirement per se in

epidemiological risk prediction, we looked for and synthesized data to align with patients' interests. We further distinguished modifiable and non-modifiable predictors of diabetes complications to potentially help improve the awareness of patients and clinicians concerning what modifiable predictors should be targeted in secondary prevention to foster optimal diabetes management. Our findings align with previous work and clinical guidelines recommending that people with diabetes maintain a healthy lifestyle, tight self-management of diabetes and hypertension, updated specific knowledge on diabetes complications and perform regular screenings for the early detection of macro and microvascular diseases.[18,130,134] Consequently, it may foster patients' self-management and well-being by reinforcing a clear sense of what predictors contribute to adverse outcomes in diabetes, while also pointing to quantitative estimates of the extent to which different predictors contribute. While many people living with diabetes may already be aware that, for example, lower HbA1c is associated with lower risk of complications, the lack of quantitative estimates to put that risk in context may contribute to diabetes burnout and distress. We highlight that measurements of how people with diabetes are coping with the condition include items such as, "Feeling that no matter how hard I try with my diabetes, it will never be good enough," and, "Feeling worried that I will develop serious long-term complications, no matter how hard I try."[135]

Given that prediction models are increasingly being appraised and recommended for formal risk assessment in treatment decision making and clinical guidelines, our findings may contribute to support risk communication in diabetes care. Specifically, it may enhance patient-clinician communication about the predictors of complications that are easier to find in the patient's chart or to access directly by the patient or the clinician. It may also help clinicians better identify people who need more support and researchers design customizable risk prediction tools for use in diabetes care.[136]

Other limitations of existing models

Overall, selected models include only a subset of well-known risk factors of diabetes complications in predictors' assessment and selection. For example, observational studies suggest that fracture risk increases with disease duration and poor glycemic control,[137] but the single study on this topic did not included disease duration or glycemic control as candidate predictors.[66] Also, severe hypoglycemia in persons with type 2 diabetes has diverse predictors: intensive glucose control, hypoglycemic medication, history of hypoglycemia or microvascular complications or dementia, renal insufficiency and longer diabetes duration.[115] However, none of the studies and models on this topic included all these factors as candidate predictors. Furthermore, the United Kingdom Prospective Diabetes Study (UKPDS) risk prediction model for cardiovascular conditions used as a basis of many of the included models does not include any measure of renal function, glycaemic control or stage or severity of diabetes and was not always complemented by new models including these variables. Futures studies should address these gaps.

Studies in this review that did not specify or distinguish participants' diabetes type (figure 3), may contribute limited implications on diabetes care because diverse diabetes types may lead

to different diabetes complications, or may lead to similar diabetes complications but in different ways. Given inconsistencies of epidemiological studies and large trials across populations concerning predictors of diabetic retinopathy, it is now recommended to use a uniform strategy to manage common risk factors for all diabetic patients.[120] This implies that findings from studies predicting retinopathy in people with unspecified diabetes may be easily applicable to all, which may not be the cause for other complications. Specifically, approximately one-third of those with diabetes worldwide have diabetic retinopathy and/or diabetic macular edema but more people with type 1 than with type 2 may experience some form of retinopathy after 20 years of having diabetes.[138] Known risk factors of diabetic retinopathy include primarily glycaemic control, hypertension and higher systolic blood pressure,[120] and these factors were candidate or selected predictors in half or more final models. However, intensive glycaemic control represents a strong predictor of retinopathy in type 1 diabetes but seems not to be crucial in type 2 diabetes,[139] and hypertension control seems to be more important to prevent diabetic retinopathy in type 2 diabetes than it is in type 1 diabetes.[140]

In the same vein, most of the studies included in this review studied people with type 2 diabetes, which provide less knowledge applicable to people with type 1 diabetes. Specifically, it will be difficult to draw any conclusion concerning the specific risk of nerve complications, cancer, fracture, hypoglycemia and hospitalization in people with type 1 diabetes given the lack of specific validated prediction models on this group. Concerning kidney complications, given that all except two studies[46,102] predicted the risk of kidney conditions in type 2 diabetes while including the glomerular filtration rate (eGFR) and the albumin-to-creatinine ratio (ACR) as candidate predictors, our findings may potentially apply to everyone with diabetes, regardless the type. Based on a large meta-analysis of data from several countries showed that, researchers suggest that, despite higher risks for kidney complications and mortality, the relative risks of these outcomes are similar in people with and without diabetes when it includes the eGFR and the ACR.[141] A similarity between those with and without diabetes may thus implies a similarity across diabetes types.

Finally, the period of time within which researchers followed up participants to observe the onset of diabetes complications was often missing. Depending on the outcome of interest, the same period of follow-up may be considered inadequate, short or sufficient. For example, it may be inappropriate to expect severe hypoglycemia in a period of less than 6 months,[115] and a longer period of time may be necessary for the occurence of micro- and macrovascular conditions or dementia. Moreover, because studies that reported the follow-up period used a large range of duration, it limited models' comparison or quantitative synthesis. Furthermore, the duration researchers included in their statistical equation to compute the risk of diabetes complication (often called prediction time) varies greatly or was missing.[35,64,65,88,95,102,104,107,112] Although one can build prediction models using cross sectional data, the alignment of the prediction time with the probability of the outcome occurrence in longitudinal design is a strength.

Equity considerations

Although there is a plausible relationship between diabetes complications and socio-economic status (SES) through diabetes management,[142] only a few models included SES variables such as insurance[104], education,[52,59,88,102] location,[68] and income.[35,67]

A single study performed sex-specific analyses[40] despite the excess risk of many diabetes complications in one or the other sex, such as the risk of cancer that is slightly greater for women than men.[143] The mechanisms explaining sex differences remains unclear and building sex-specific models may contribute to knowledge advancement in this area.[144]

Concerning the applicability of our findings, it is important to highlight that health disparities in diabetes and its complications exist globally.[117,146] Among the 422 million people living with diabetes worldwide, about three-quarters reside in low- and middle-income countries, particularly India and China.[1] Moreover, in most high-income countries, the prevalence of type 2 diabetes among members of ethnocultural minorities is two to five times higher than in the general population.[147–149] However, most of the data included in this review were from people living in high-income or middle-income countries, and most studies reported small or no proportions of Black, Indigenous, or Hispanic people. For these reasons, included models may or may not apply to people with diabetes from minoritized populations. Furthermore, since the time between diabetes diagnosis and complications onset vary greatly between high-income and low- and middle-income countries, our findings and implications should be interpreted according to the economic status and populations targeted. Future studies on this topic should better involve minoritized and/or diverse populations to fill the lack of knowledge about the risks of diabetes complications in people of diverse backgrounds.

Methodological considerations

Risks prediction are useful to estimate a probability of having or developing one or multiple health outcomes in an individual, which refer respectively to diagnostic and prognostic prediction.[145] In some cases, especially because of a lack of details in the methods, it was not obvious to identify and distinguish diagnostic and prediction models of diabetes complications in published papers. We recommend that future papers make this distinction clear to facilitate understanding, especially in a context of patient-included and multidisciplinary research where clarity in complex information can facilitate understanding in people from diverse backgrounds.[130] Furthermore, it is increasingly recommended that prediction models be validated both internally and externally, and if both are not possible, external validation should be prioritized.[150] However, some argued that it may be disputable to validate a score generated from a randomized trial in a population derived from another randomized trial although external validation is advocated to determine generalizability to similar settings and patient population.[95]

Strengths and limitations of this review

This review has four main strengths. First, we integrated diverse perspectives of patients, clinicians and researchers regarding this topic. Additionally to the five patient partners that

we consulted, two people living with type 1 and type 2 diabetes (SD, DG) contributed in this work as co-authors to complement the perspective of the senior author (HOW) who lives with type 1 diabetes. We also collaborated with caregivers and clinicians to enhance the results and make them more useful to policy makers, practitioners and service users.[30] Second, we included diverse diabetes complications to respond to patients' and caregivers' information needs. Third, we restricted this review to longitudinal study designs that allow to efficiently predict the onset of diabetes complications and to strengthen our interpretation of cause-effect association.[4,22] Moreover, including retrospective cohorts allowed us to capture outcomes that require a long-term period of time for enough events to occur,[151] which are of great importance to improve diabetes care and lives. Fourth, although the central message in prediction models is about accuracy (discrimination and calibration) rather than risk factors, and because relying on prediction models that are highly biased may have disastrous consequences on people's living with diabetes, we intentionally assessed epidemiological bias and potential impacts on selected prediction models.[152–154]

This review has two main limitations. First, our search strategy did not include grey literature. Second, we were unable to perform a meta-analysis because there were not enough (n>5) high quality models with comparable methodological features among included models. Heterogeneity is one of the main reasons for not doing meta-analyses of non-experimental studies,[22,155] which represent the great majority of studies on this topic.[5,156] Merging very diverse models often lead to highly correlated data and inflation in the estimates of variance.[157,158] We therefore elected to use a systematic narrative approach to synthesize our findings.[159]

Conclusion

This review showed that existing prediction models of diabetes complication concern a broad range of health conditions. However, there is a lack of predictive models for important patient groups as well as for relevant complications and existing models only partly align with prevalent and patient-important complications. Patients reported receiving frequent instructions of what to do and fear-based, simplistic messaging about complications. Our comprehensive and rigorous knowledge synthesis may serve to enhance shared-decision making about preventive strategies for diabetes complications. Future studies should address as yet unmet needs for analyses of certain complications and patient groups, and should consistently assess and report external validation and all relevant statistics of models' performance. Our next steps will include translating models showing the extent of potential risk reductions in understandable ways into patient communication and decision-making materials.

Figure 2: Numbers of prediction models per year of publication

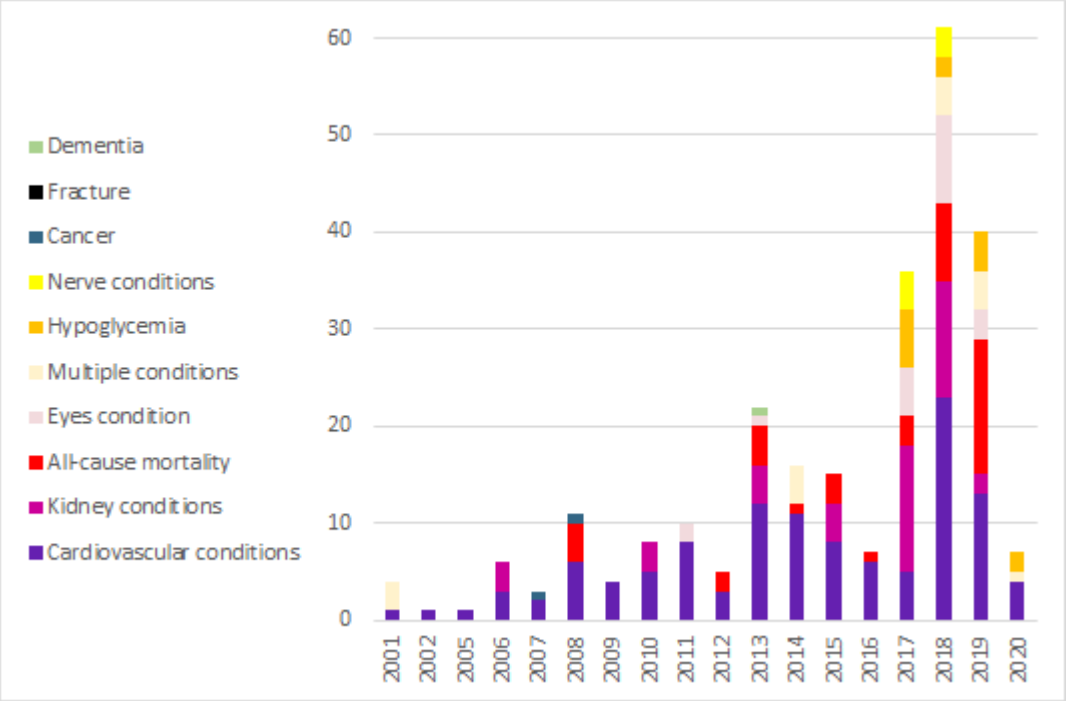
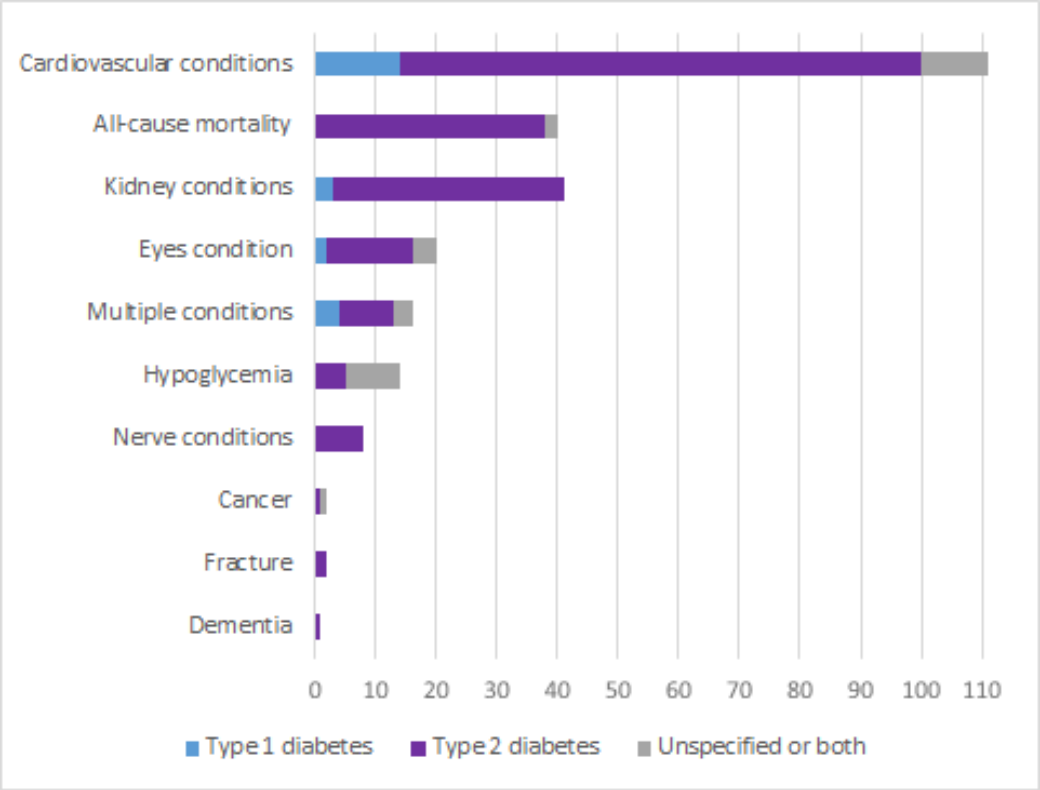


Figure 3: Numbers of prediction models by outcomes and by diabetes type



Tables

Table 1: Predictors include in selected studies

	First author	**Complications**	**Number of models***	**Number of selected predictors ****	Non Modifiable factors **(Demographic)**	Partly modifiable factor**s** **(Health conditions)**	Modifiable factor**s** **(Clinical characteristics)**
Cardiovascular	Aminian et al., 2019	Cardiovascular disease	2	28	Age, sex, race	Dyslipidemia, Peripheral neuropathy, Heart failure, Coronary artery disease, COPD, Nephroprathy, Periphera arterial disease, Cerebrovascular disease, Dyalisis, Hypertension	BMI (kg/m2), BMI category (kg/m2), systolic blood pressure,
Cardiovascular	Aminian et al., 2019	Heart failure	2	28	Age, sex; race	Dyslipidemia, Peripheral neuropathy, Heart failure, Coronary artery disease, COPD, Nephroprathy, Periphera arterial disease, Cerebrovascular disease, Dyalisis, Hypertension	BMI (kg/m2), BMI category (kg/m2), systolic blood pressure,
Cardiovascular	Arnold et al., 2016	Coronary artery disease with chest pain (angina)/acute coronary syndrome	1	8	Age, Nonwhite race, sex	Prior bypass graft surgery, Chronic heart failure	
Cardiovascular	Basu S., 2017	atherosclerotic cardiovascular disease	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure

Cardiovascular	Basu S., 2017	fatal or non-fatal myocardial infarction	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Cardiovascular	Basu S., 2017	fatal or non-fatal stroke	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Cardiovascular	Basu S., 2017	congestive heart failure	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Cardiovascular	Basu S., 2017	death from any cardiovascular cause	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Cardiovascular	Basu S. et al., 2018	Cardiovascular outcome (composite ASCVD; fatal or nonfatal MI; fatal or nonfatal stroke; Coronary heart failure)	2	11	-	peripheral vascular disease, atrial fibrillation	systolic blood pressure, BMI,
Cardiovascular	Basu S. et al., 2018	Nephropathy; Diabetic retinopathy; Cardiovascular outcome	2	14	Age, sex, race		Systolic blood pressure
Cardiovascular	Berkelmans 2019	Cardiovascular disease	3	11	Sex	Albuminuria, history of CVD	BMI, duration of T2DM, SBP
Cardiovascular	Cederholm et al., 2008	Cardiovascular disease	2	9	Sex		BMI, Age at onset of diabetes, duration of diabetes, systolic blood pressure
Cardiovascular	Cederholm et al., 2011	Cardiovascular disease	6	8		Macroalbuminuria; Previous CVD	Diabetes duration; Onset age of diabetes, systolic blood pressure
Cardiovascular			1	8	Age, sex,	Microalbuminuria	

	Christianson et al., 2006	Coronary Heart Disease					Duration of diabetes, systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	6	Age, sex		systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	7	Age, sex		systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	7	Age, sex		systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	8	Age, sex		systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	8	Age, sex		diabetes status, systolic blood pressure
Cardiovascular	Colombo et al., 2018	Cardiovascular disease	1	10	Age, sex		diabetes status, systolic blood pressure
Cardiovascular	Davis et al., 2009	Cardiovascular disease	4	n/a			
Cardiovascular	Davis et al., 2010	Cardiovascular disease	1	8	Age, sex, Southern European; Indigenous Australian	Prior CVD	
Cardiovascular	Donnan et al., 2006	Major coronary heart disease	1	9	Sex		height, Duration of diabetes, age at diagnosis of diabetes, systolic blood pressure
Cardiovascular	Elley et al., 2010	Cardiovascular disease	2	9	Age, gender, ethnicity		Duration of known diabetes, systolic BP
Cardiovascular	Garcia-Carretero 2019	Major adverse cardiovascular event	1	4	Gender		BMI
Cardiovascular	Guzder et al., 2005	Coronary heart disease	1	n/a			

Cardiovascular	Hippisley-Cox et al., 2015	Heart failure	4	13	Age, ethnicity	atrial fibrillation, cardiovascular disease and chronic renal disease	BMI, duration and type of diabetes, systolic blood pressure
Cardiovascular	Kengne et al., 2011	Cardiovascular disease	1	10	Sex	retinopathy, atrial fibrillation	Age at diagnosis, known duration of diabetes
Cardiovascular	Kothari et al., 2002	Stroke	1	7	sex	atrial fibrillation	Duration of diagnosed diabetes, age at diagnosis of diabetes, systolic blood pressure
Cardiovascular	Li, T. et al., 2018	Ischemic stroke	3	14	Age, gender	Arterial embolism and thrombosis; Diabetes retinopathy; Hypoglycemia	duration of type 2 diabetes, Blood pressure (mm Hg)
Cardiovascular	Looker et al., 2015	Acute Coronary Heart Disease	1	8	Age, sex		diabetes status, systolic blood pressure
Cardiovascular	Looker et al., 2015	Acute Coronary Heart Disease	1	18	Age, sex, cohort		diabetes duration, height, BMI, systolic and diastolic blood pressure
Cardiovascular	Looker et al., 2015	Acute Coronary Heart Disease	1	24	Age, sex, cohort		diabetes duration, BMI, height, systolic and diastolic blood pressure
Cardiovascular	Looker et al., 2015	Acute Coronary Heart Disease	1	18	Age, sex, cohort		diabetes duration, height, BMI, systolic and diastolic blood pressure
Cardiovascular	Lyu 2020	Acute myocardial infarction	1	10	age	hypertension history	BMI, diabetes mellitus duration, SBP, DBP

Cardiovascular	McEwen et al., 2012	Cardiovascular death	1	16	Age, race, sex, income	history of nephropathy, history of TIA-stroke or endarterectomy, history of (angina, myocardial infarction, other coronary heart disease, coronary angioplasty, or coronary bypass), history of peripheral vascular disease or peripheral vascular surgery	BMI
Cardiovascular	Mukamal et al., 2013	Cardiovascular disease	3	8	Age		Systolic BP per 10 mmHg up to 160
Cardiovascular	Mukamal et al., 2013	Cardiovascular disease	1	9	Age		Systolic BP per 10 mmHg up to 160
Cardiovascular	Mukamal et al., 2013	Cardiovascular disease	3	12	Age	ECG left ventricular hypertrophy	Systolic BP per 10 mmHg up to 160
Cardiovascular	Pfister et al., 2013	Heart failure	1	12	Age	right and left bundle branch block, microalbuminuria, previous myocardial infarction	duration of diabetes, heart rate
Cardiovascular	Pinies et al., 2014	Cardiovascular disease	3	6	Sex		Age at diagnosis, SBP
Cardiovascular	Pinies et al., 2014	Coronary heart disease	3	4	Sex		Age at diagnosis
Cardiovascular	Pinies et al., 2014	Coronary heart disease	3	n/a			
Cardiovascular	Qintar 2019	Major adverse cardiovascular event	2	9	Age	History of MI, History of stroke	
Cardiovascular	Qintar 2019	Coronary artery disease with chest pain (angina)/acute	1	7	Age, sex	ACS vs stable CAD, Angina at BL: Daily/Weekly vs. No Angina at BL,	

		coronary syndrome					
Cardiovascular	Robinson et al., 2012	Cardiovascular disease	1	9	sex, ethnicity	presence of micro or macroalbuminuria	Age at diagnosis, duration of diabetes, systolic blood pressure
Cardiovascular	Robinson et al., 2012	Cardiovascular disease	1	10	sex, ethnicity	presence of micro or macroalbuminuria	Age at diagnosis, duration of diabetes, systolic blood pressure
Cardiovascular	Stevens et al., 2001	Coronary heart disease	1	7	Age, sex, race		SBP
Cardiovascular	Shao 2018	Stroke	1	6		MI history, stroke history	age at diagnosis, SBP
Cardiovascular	Shao 2018	Heart failure	1	9	education	Severe hypoglycemia, MI history, CHF history, revascularisation history	BMI, age at diagnosis, SBP
Cardiovascular	Shao 2018	Myocardial infarction	1	11	sex, education, race	Severe hypoglycemia, MI history, CHF history, stroke history	Age at diagnosis
Cardiovascular	Shao 2018	Coronary artery disease with chest pain (angina)/acute coronary syndrome	1	7		severe hypoglycemia, MI history, angina history, revascularisation history	BMI
Cardiovascular	Shao 2018	Revascularisation surgery	1	9	sex, race	stroke history, angina history, revascularisation history	BMI, BMI^2, SBP
Cardiovascular	Shao 2018	Cardiovascular death	1	9		MI history, CHF history, stroke history, stroke event, CHF event	BMI, duration of diabetes, SBP
Cardiovascular	Tanaka et al., 2013	Coronary heart disease	1	6	Sex, age		SPB
Cardiovascular	Tanaka et al., 2013	Stroke	1	7	Sex, age	Atrial fibrillation	SBP

Cardiovascular	Tanaka et al., 2013	Coronary heart disease	1	n/a			
Cardiovascular	Tanaka et al., 2013	Stroke	1	n/a			
Cardiovascular	Vistisen et al., 2016	Cardiovascular disease	5	10	Age, sex	Albuminuria	diabetes duration, systolic blood pressure
Cardiovascular	Wan et al., 2018	Cardiovascular disease	1	20	Age		duration of T2DM, BMI; BMI2, SBP; SBP2; DBP; DBP2;
Cardiovascular	Wan et al., 2018	Cardiovascular disease	1	10	Age		SBP; SBP2;
Cardiovascular	Wan et al., 2018	Cardiovascular disease	1	19	Age		duration of T2DM, BMI; BMI2, SBP; DBP; DBP2
Cardiovascular	Williams 2020	Heart failure	1	9	Age	coronary artery disease, atrial fibrillation, chronic kidney disease	Systolic blood pressure
Cardiovascular	Williams 2020	Heart failure	1	14	Age	coronary artery disease, atrial fibrillation, chronic kidney disease, anemia, cardiomyopathy, dyspnea, hyperlipidemia	Systolic blood pressure
Cardiovascular	Williams 2020	Heart failure	1	15	Age	coronary artery disease, atrial fibrillation, chronic kidney disease	Systolic blood pressure
Cardiovascular	Wan et al., 2018	Cardiovascular disease	1	9	Age		SBP; SBP2
Cardiovascular	Yang et al., 2007	Stroke	1	4	Age	history of coronary heart disease (CHD)	
Cardiovascular	Yang et al., 2007	Stroke	1	6	Age, sex		Systolic blood pressure
Cardiovascular	Yang et al., 2008a	Heart failure hospitalisation	1	6	Age	CHD event during follow-up	BMI
Cardiovascular	Yang et al., 2008d	circulatory death	1	9			

Cardiovascular	Yang et al., 2008b	Coronary heart disease	1	7	Age, sex		Duration of diagnosed diabetes, age at diagnosis of diabetes, systolic blood pressure
Cardiovascular	Yang et al., 2008b	Coronary heart disease	1	6	Age, sex		Systolic blood pressure
Cardiovascular	Yeboah et al., 2014	Coronary heart disease	1	5	Age, sex		duration of diabetes, systolic blood pressure
Cardiovascular	Yeboah et al., 2014	Coronary heart disease	1	n/a			
Cardiovascular	Yang et al. 2020	Atrial Fibrillation	1	11	Age, gender, race	Heart failure	BMI, duration of diabetes, diastolic blood pressure
Cardiovascular	Yu 2019	Cardiovascular death	1	27	Gender, (Age/10)3, (Age/10)3×ln(age/10)		(Body mass index/10)3, (Body mass index/10)3×ln(body mass index/10), Systolic blood pressure ≥150 mm Hg, Diastolic blood pressure ≥90 mm
Cardiovascular	Zethelius et al., 2011	Cardiovascular disease	1	12	sex	Microalbuminuria; Macroalbuminuria; Atrial fibrillation; Previous CVD	Onset age; Diabetes duration, Log of BMI; Log of Systolic BP
Cardiovascular	Zgibor et al., 2006	Coronary heart disease	1	7	Age, sex, race		SBP
Cardiovascular	Zgibor et al., 2010	Coronary heart disease	2	4		micro or macroalbuminuira	longer diabetes duration
Kidney	Aminian et al., 2019	Nephropathy	2	28	Sex, age, race	Hypertension; Dyslipidemia; Peripheral neuropathy; Heart failure; Coronary artery disease; COPD; Nephroprathy; Peripheraarterial disease; Cerebrovascular disease; Dyalisis	BMI, BMI category, systolic blood pressure

Kidney	Basu S., 2017	Nephropathy	3	15	Age, sex, ethnicity	history of cardiovascular disease	BMI, blood pressure
Kidney	Basu S., 2017	Nephropathy	3	14	Age, sex, ethnicity	history of cardiovascular disease	BMI, blood pressure
Kidney	Basu S et al., 2018	Nephropathy	6	14	Age, sex, ethnicity		BMI, systolic blood pressure
Kidney	Basu S et al., 2018	Nephropathy	2	11		peripheral vascular disease, atrial fibrillation	BMI, systolic blood pressure, heart rate
Kidney	Dagliati et al., 2018	Kidney failure/chronic renal failure	3	4			BMI
Kidney	Dorajoo et al., 2017	Albuminuria	2	4		Hypertension	
Kidney	Dunkler et al., 2015	Chronic kidney disease	2	5	Sex, age	albuminuria stage (normo- or microalbuminuria)	
Kidney	Dunkler et al., 2015	Chronic kidney disease	2	15	sex, age, race	albuminuria stage, the comorbidities major atherosclerotic cardiac events, stroke or transient ischemic attack, peripheral artery disease	waist circumference, diabetes duration
Kidney	Elley et al., 2013	End-stage renal disease	1	6	Sex, ethnicity	albuminuria	Age of onset of diabetes, duration of diabetes
Kidney	Elley et al., 2013	End-stage renal disease	1	9	Sex, ethnicity	albuminuria, history of CVD	Age of onset of diabetes, duration of diabetes, systolic BP
Kidney	Elley et al., 2013	End-stage renal disease	1	10	Sex, ethnicity	albuminuria, history of CVD	Age of onset of diabetes, duration of diabetes, systolic BP
Kidney	Miao et al., 2017	Diabetic nephropathy	2	8	Age, Location	Hypertension or dyslipidemia; Retinopathy	BMI

Kidney	Peters et al., 2017	Renal function decline	1	8	Age		diabetes duration
Kidney	Tanaka et al., 2013	Overt nephropathy	1	5		Atrial fibrillation	SBP
Kidney	Shao et al.,2018	End-stage renal disease	1	4		CHF history, blindness history	SBP
Kidney	Vergouwe et al., 2010	Microalbuminuria	3	5			BMI, WHR
Kidney	Wan, E. et al., 2017a	End-stage renal disease	1	16	Age		SBP; DBP; DBP2
Kidney	Wan, E. et al., 2017a	End-stage renal disease	1	17	Age		duration of T2DM, BMI; BMI2, SBP; DBP; DBP2
Kidney	Yang et al., 2006	End-stage renal disease	1	4		Retinopathy	Known duration of diabetes, systolic BP
Kidney	Yang et al., 2006	End-stage renal disease	1	3			
Kidney	Yang et al., 2006	End-stage renal disease	1	4			
Mortality	Arnold et al., 2016	All-cause mortality	1	13	Age	Left ventricular systolic dysfunction, chronic heart failure, chronic lung disease, prior myocardial infarction	Body mass index
Mortality	Aminian et al., 2019	All-cause mortality	2	28	Sex, age, race	Hypertension; Dyslipidemia; Peripheral neuropathy; Heart failure; Coronary artery disease; COPD; Nephroprathy; Peripheraarterial disease; Cerebrovascular disease; Dyalisis	BMI, BMI category, systolic blood pressure
Mortality	Basu S et al., 2017	all-cause mortality	1	14	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure

Mortality	Basu et al., 2018	Nephropathy; Diabetic retinopathy; Cardiovascular outcome	2	14	Age, sex, race		Systolic blood pressure
Mortality	Berkelmans et al., 2019	Non vascular mortality	4	11	Sex	Albuminuria, history of CVD	BMI, duration of T2DM, SBP
Mortality	Copetti 2019	All-cause mortality	4	9	Age		BMI, diastolic blood pressure
Mortality	Copetti 2019	All-cause mortality	2	14	Age	history of documented nonfatal myocardial infarction, stroke, retinopathy	BMI, diastolic blood pressure
Mortality	Copetti 2019	All-cause mortality	2	Not reported			
Mortality	De Cosmo et al., 2013	All-cause mortality	3	9	Age		BMI, Diastolic blood pressure
Mortality	Li et al., 2018	In-hospital mortality	4	13	Age, Gender	Stroke; Diabetes retinopathy; Hypertension; Hypoglycemia	
Mortality	McEwen et al., 2012	Non-vascular mortality	1	8	Age, sex, income	history of nephropathy, history of congestive heart failure, history of angina, myocardial infarction, other coronary heart disease, coronary angioplasty or coronary bypass,	
Mortality	McEwen et al., 2012	All-cause mortality	1	16	Age, sex, income	history of nephropathy, history of congestive heart failure	
Mortality	Robinson et al., 2015	All-cause mortality	1	10	sex, Maori, Pacific, East Asian, Indo Asian, Other		Age of onset (10 years), Age of onset squared, Duration (10 years), Duration squared

Mortality	Robinson et al., 2015	All-cause mortality	1	20	sex, Maori, Pacific, East Asian, Indo Asian, Other	History of CVD	Age of onset (10 years), Age of onset squared, Duration (10 years), Duration squared, BMI (per 10 kg/m2), BMI squared, Systolic BP (per 10 mmHg), Systolic BP squared,
Mortality	Robinson et al., 2015	All-cause mortality	1	25	sex, Maori, Pacific, East Asian, Indo Asian, Other	History of CVD, Microalbuminuria, Macroalbuminuria, Advanced albuminuria	Age of onset (10 years), Age of onset squared, Duration (10 years), Duration squared, BMI (per 10 kg/m2), BMI squared, Systolic BP (per 10 mmHg), Systolic BP squared,
Mortality	Savonitto et al., 2018	All-cause mortality	1	8	Age	lack of coronary revascularization, prior coronary artery bypass, prior myocardial infarction	heart rate
Mortality	Shao et al., 2018	All-cause mortality	1	14	Sex, education	MI history, CHF history, stroke history, angina history, revascularisation history, stroke event, CHD event	duration of diabetes, BMI
Mortality	Tanaka et al., 2013	Noncardiovascular mortality	1	6	Sex, age		BMI (<18.5/18.5–25 kg/m2); BMI (>25/18.5–25 kg/m2)
Mortality	van Diepen et al., 2014	All-cause mortality	1	7	Age	history of macrovascular complications	duration of DM
Mortality	Yang et al., 2008d	All-cause mortality	1	9	Age, sex	peripheral arterial disease, cancer history	BMI
Mortality	Yang et al., 2008d	genitourinary death	1	9	Age, sex	peripheral arterial disease, cancer history	BMI

Mortality	Yang et al., 2008d	respiratory death	1	9	Age, sex	peripheral arterial disease, cancer history	BMI
Mortality	Yang et al., 2008d	neoplasm death	1	9	Age, sex	peripheral arterial disease, cancer history	BMI
Mortality	Wan, E. et al., 2017b – model 1	All-cause mortality	1	20	Age		BMI; BMI2; SBP; SBP2
Mortality	Wan, E. et al., 2017b – model 2	All-cause mortality	1	25	Age		duration of T2DM, BMI; BMI2, SBP; SBP2; DBP; DBP2
Eyes	Basu S et al., 2017	Retinopathy	2	12	Age, sex, ethnicity	history of cardiovascular disease	BMI, blood pressure
Eyes	Basu S et al., 2017	Retinopathy	3	13	Age, sex, ethnicity	history of cardiovascular disease	BMI, blood pressure
Eyes	Basu et al., 2018	Nephropathy; Diabetic retinopathy; Cardiovascular outcome	2	14	Age, sex, race		Systolic blood pressure
Eyes	Basu et al., 2018	Nephropathy; Diabetic retinopathy; Cardiovascular outcome	2	11		peripheral vascular disease, atrial fibrillation	BMI, heart rate, Systolic blood pressure
Eyes	Dagliati et al., 2018	Diabetic retinopathy	3	5			Time to diabetes diagnostic, BMI
Eyes	Garcia-Finana et al., 2019	Retinopathy	1	3			Duration of diabetes
Eyes	Garcia-Finana et al., 2019	Retinopathy	1	4			Duration of diabetes, type 1 diabetes, systolic blood pressure
Eyes	Harrison et al., 2011a	Diabetic retinopathy	1	2			Duration of diabetes

Eyes	Harrison et al., 2011b	Diabetic edema (or macular edema)	1	3			
Eyes	Kang 2018	Retinopathy	1	4	sex		Onset of type 1 diabetes at age 5–14 yrs, duration of T1DM
Eyes	Schreur 2019	Retinopathy	1	6	sex	presence of a less severe form of DR	diabetes type, duration of diabetes, SBP at baseline
Eyes	Shao 2018	Blindness	1	7	education, race	Severe hypoglycemia	age at diagnosis, SBP
Eyes	Tanaka et al., 2013	Retinopathy	1	6	Age		BMI (<18.5/18.5–25 kg/m2); BMI (>25/18.5–25 kg/m2, years after diagnosis
Hypoglycemia	Chow 2018	Hypoglycemia	1	17	Age, race, education	history of hypoglycemia in the last week	waist circumference, years since diabetes diagnosis, systolic blood pressure, diastolic blood pressure
Hypoglycemia	Han 2018	Hypoglycemia	1	14	Age, sex	hypertension, Chronic kidney disease, previous SH history within the past 3 years	BMI, duration of diabetes
Hypoglycemia	Karter et al., 2017	Hypoglycemia	2	6	age younger than 77 years	Total number of prior episodes of hypoglycemia related ED or hospital utilization, number of ED encounters for any reason in the prior 12 months, presence of severe or end-stage kidney disease	

Hypoglycemia	Li 2019	Hypoglycemia	3	21	Age, gender, race, insurance	Autonomic failure, Cancer, Chronic heart failure, Coronary artery disease, Dementia or falls, Diabetic neuropathy, Infection within 30 days, Hypoglycemia within 12 months	BMI
Hypoglycemia	Mueller 2020	Hypoglycemia	1	388	13 demographic variables	89 diagnosis variables	
Hypoglycemia	Schroeder et al., 2017	Severe hypoglycemia	2	16	Age; Race/ethnicity	Severe hypoglycemia within the previous 365 days; Retinopathy; Cardiovascular disease; Depression; Heart failure	Type 1 diabetes; Body mass index
Hypoglycemia	Schroeder et al., 2017	Severe hypoglycemia	2	6	Age	history of a hypoglycemic event in the prior 365 days	diabetes type (type 1 or 2)
Hypoglycemia	Shah 2019	Hypoglycemia	1	5	Age	emergency department visit during the 6 months prior, severe chronic kidney disease	
Hypoglycemia	Weiner 2020	Hypoglycemia	1	17	African-American, Hispanic, age 75 or more years.	eating disorder, infection within 30 days, previous HG within 12 months, diabetic neuropathy, chronic heart failure, dementia or falls	
Nerve	Dagliati et al., 2018	Diabetic neuropathy	3	4			BMI, Time to diabetes diagnostic
Nerve	Basu et al., 2017	Neuropathy	3	12	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Nerve	Basu et al., 2017	Neuropathy	1	11	Age, sex, ethnicity	history of cardiovascular disease	Blood pressure
Nerve	Shao et al., 2018	Diabetic peripheral	1	7	sex, race	blindness history	age at diagnosis, SBP

		neuropathy (DPN)					
Cancer	Boursi et al., 2017	Pancreatic cancer	1	11	Age		body mass index (BMI), change in BMI per year
Cancer	Yang et al., 2008c	All-site cancer	1	4	Age		
Fracture	Martinez-Laguna 2018	Fracture	1	5	Age, sex	previous major fracture, previous IHD (ischemic heart disease)	
Fracture	Martinez-Laguna 2018	Fracture	1	6	Age, sex	previous major fracture, previous stroke	
Cognitive problems	Exalto et al., 2013	Dementia	1	8	Age, education	Microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, depression	
Other complications	Li et al., 2018	Diabetes-related hospitalization	4	14	Gender	Stroke; Diabetes retinopathy	Duration of type 2 diabetes, Body mass index
Other complications	Mueller et al., 2020	type 2 diabetes-related inpatient admission	1	388	13 demographic variables	89 diagnosis variables	
Other complications	Selby et al., 2001	Macro and microvascular complications	1	16	Age, education, sex	Outpatient diagnoses, Inpatient events, outpatient diagnosis, outpatient diagnoses, self-report of neuropathy	type of diabetes
Other complications	Selby et al., 2001	Metabolic complications	1	12	Age, race, sex	Inpatient metabolic events, Inpatient M/M events	obesity status
Other complications	Selby et al., 2001	Infectious complications	1	8	Age	Impatient events, outpatient M/M diagnoses, outpatient ID diagnoses	

Other complications	Berkelmans et al., 2019	Cardiovascular disease, Non-cardiovascular mortality	4	11	Sex	Albuminuria, history of Cardiovascular diseases	Body mass Index, duration of type 2 diabetes, Systolic blood pressure
Other complications	Soedamah-Muthu et al., 2014	First incident major outcomes	4	5	Age		Weight-Heigth ratio

Table 1: Predictors include in selected studies (Continued)

	First author	Modifiable factors **(Medication)**	Modifiable factors **(Lab tests)**	Modifiable factor **(Lifestyle factors)**	**Other**
Cardiovascular	Aminian et al., 2019	Lipid-lowering medications, Renin-angiotensin system inhibitors, Other antihypertensive medications, Aspirin, Warfarin, Noninsulin diabetes medications, Insulin	HcA1c, eGFR, LDL, Triglycérides	Smoking status	
Cardiovascular	Aminian et al., 2019	Lipid-lowering medications, Renin-angiotensin system inhibitors, Other antihypertensive medications, Aspirin, Warfarin, Noninsulin diabetes medications, Insulin	HcA1c, eGFR, LDL, Triglycérides	Smoking status	
Cardiovascular	Arnold et al., 2016			Currently working, current smoker	SAQ Angina Frequency
Cardiovascular	Basu S., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking	

Cardiovascular	Basu S., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking
Cardiovascular	Basu S., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking
Cardiovascular	Basu S., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking
Cardiovascular	Basu S., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking
Cardiovascular	Basu S. et al., 2018		HbA1c, HDL cholesterol, LDL cholesterol, estimated GFR (eGFR), heart rate, white blood cell count, Haemoglobin	
Cardiovascular	Basu S. et al., 2018	Current use of statin, oral diabetes medications including metformin, and anticoagulants other than aspirin	Total cholesterol, HDL cholesterol, urine creatinine, urine microalbuminto-creatinine ratio, and hemoglobin A1c	Current tobacco smoking
Cardiovascular	Berkelmans 2019	insulin treatment	HbA1c, eGFR, non-HDL-c	Current smoking
Cardiovascular	Cederholm et al., 2008	Antihypertensive drugs, Lipid-Lowering drugs		Smoking
Cardiovascular	Cederholm et al., 2011		TC:HDL, HbA1c	Smoker
Cardiovascular	Christianson et al., 2006		HBA1C level; Lipid ratio (Total Cholesterol/HDL)	Smoking
Cardiovascular	Colombo et al., 2018		total cholesterol, HDL-C	smoking status
Cardiovascular	Colombo et al., 2018		Apolipoprotein CIII (ApoCIII), total cholesterol, HDL-C	smoking status

Cardiovascular	Colombo et al., 2018		N-terminal prohormone b-type natriuretic peptide, total cholesterol, HDL-C	smoking status	
Cardiovascular	Colombo et al., 2018		Apolipoprotein CIII (ApoCIII), N-terminal prohormone b-type natriuretic peptide, total cholesterol, HDL-C	smoking status	
Cardiovascular	Colombo et al., 2018	antihypertensive medication use	total cholesterol, HDL-C	current smoking	
Cardiovascular	Colombo et al., 2018	antihypertensive medication use	Apolipoprotein CIII (ApoCIII); N-terminal prohormone b-type natriuretic peptide, total cholesterol, HDL-C	Current smoking	
Cardiovascular	Davis et al., 2009				
Cardiovascular	Davis et al., 2010		urinary albumin : creatinine ratio, HbA1c, serum HDL-cholesterol		
Cardiovascular	Donnan et al., 2006	Treated hypertension	Total cholesterol, HbA1c	Smoking status	
Cardiovascular	Elley et al., 2010		TC:HDL ratio, HbA1c, ACR	Smoking status	
Cardiovascular	Garcia-Carretero 2019	T2DM	PWV		
Cardiovascular	Guzder et al., 2005				
Cardiovascular	Hippisley-Cox et al., 2015		cholesterol/HDL ratio, HbA1c	Smoking	Material deprivation
Cardiovascular	Kengne et al., 2011	Treated hypertension	Pulse pressure, HbA1c; Log of urinary albumin/creatinine ratio; Non-HDL cholesterol;		
Cardiovascular	Kothari et al., 2002		lipid ratio total: HDL cholesterol	smoking at diagnosis of diabetes	
Cardiovascular	Li, T. et al., 2018	Anti-diabetes medications, Cardiovascular medications	HbA1c level (%); TC to HDL ratio; Creatinine (mg/dL) abnormal; Fasting plasma glucose variation (FPG-CV)	Smoking habit	
Cardiovascular	Looker et al., 2015	antihypertensive medication use	total cholesterol, HDL-C	Current smoking	
Cardiovascular	Looker et al., 2015	current medication (including antihypertensive agents, aspirin, lipid- lowering agents and insulin).	LDL- cholesterol (LDL-C), HDL-cholesterol (HDL-C), triacylglycerol, HbA1c, estimated GFR (eGFR)	Smoking	

Cardiovascular	Looker et al., 2015	current medication (including antihypertensive agents, aspirin, lipid- lowering agents and insulin)	LDL- cholesterol (LDL-C), HDL-cholesterol (HDL-C), triacylglycerol, HbA1c, estimated eGFR, NT-proBNP, apoCIII, hsTnT, IL-6, sRAGE, IL-15	Smoking	
Cardiovascular	Looker et al., 2015	current medication (including antihypertensive agents, aspirin, lipid- lowering agents and insulin).	LDL- cholesterol (LDL-C), HDL-cholesterol (HDL-C), triacylglycerol, HbA1c, estimated GFR (eGFR)	Smoking	LASSO penalised regression selected biomarkers (Data not shown)
Cardiovascular	Lyu 2020		LDL-C, SUA, Lp(a)	alcohol drinking status	
Cardiovascular	McEwen et al., 2012	Treatment of diabetes, use of diuretics, use of beta blockers, use of other antihypertensive, use of cholesterol-lowering medications	LDL choleserol	Smoking	
Cardiovascular	Mukamal et al., 2013	Oral hypoglycaemic agent or insulin use	total cholesterol, HDL cholesterol, Creatinine >110.5 μmol/l	Former smoker, current smoker	
Cardiovascular	Mukamal et al., 2013	Oral hypoglycaemic agent or insulin use	total cholesterol, HDL cholesterol, Creatinine >110.5 μmol/l, CRP per 10 nmol/l up to 190 nmol/l	Former smoker, current smoker	
Cardiovascular	Mukamal et al., 2013	Oral hypoglycaemic agent or insulin use	total cholesterol, HDL cholesterol, Creatinine >110.5 μmol/l, CRP per 10 nmol/l up to 190 nmol/l, ABI <1, Internal carotid IMT per mm up to 3	Former smoker, current smoker	
Cardiovascular	Pfister et al., 2013	Diuretic use, pioglitazone treatment	elevated serum creatinine, HbA1c, LDL cholesterol		
Cardiovascular	Pinies et al., 2014		Non-HDL:HDL; HbA1c at diagnosis	Tobacco	
Cardiovascular	Pinies et al., 2014		Non-HDL:HDL; HbA1c at diagnosis		
Cardiovascular	Pinies et al., 2014				
Cardiovascular	Qintar 2019	Insulin	eGFR, LVEF	History of smoking	Syntax >22, treatment interaction with a history of smoking

Cardiovascular	Qintar 2019		Hemoglobin		treatment interaction with SYNTAX score, Monthly vs. No Syntax >22 (PCI), Syntax >22 (CABG)
Cardiovascular	Robinson et al., 2012		HbA1c, total cholesterol: HDL cholesterol ratio (TC/HDL)	smoking status	
Cardiovascular	Robinson et al., 2012	Current antihypertensive treatment	HbA1c, total cholesterol: HDL cholesterol ratio (TC/HDL)	smoking status	
Cardiovascular	Stevens et al., 2001		HbA1c, Total cholesterol/HDL cholesterol ratio	Smoking	
Cardiovascular	Shao 2018		HbA1c, LDL		
Cardiovascular	Shao 2018		HbA1c		
Cardiovascular	Shao 2018		HbA1c, LDL	Smoking	
Cardiovascular	Shao 2018		HbA1c, LDL		
Cardiovascular	Shao 2018		HbA1c		
Cardiovascular	Shao 2018		HbA1c	Smoking	
Cardiovascular	Tanaka et al., 2013		HbA1c, NHDL-C	Current smoker	
Cardiovascular	Tanaka et al., 2013		HbA1c, NHDL-C	Leizure time physical activity (LTPA)	
Cardiovascular	Tanaka et al., 2013				
Cardiovascular	Tanaka et al., 2013				
Cardiovascular	Vistisen et al., 2016		low-density lipoprotein cholesterol, hemoglobin A1c, glomerular filtration rate	Smoking, exercice	
Cardiovascular	Wan et al., 2018	Anti-hypertensive drugs used; Insulin drug	HbA1c, TC/HDL-C ratio; ln(urine ACR + 1); eGFR (60 to 89 mL/min/1.73 m2); eGFR (30 to 59 mL/min/1.73 m2); eGFR (<30 mL/min/1.73 m2)	Smoker	Age interaction term (Age × smoker); Age interaction term

					(Age × HbA1c); Age interaction term (Age × TC/HDL-C ratio)
Cardiovascular	Wan et al., 2018		HbA1c, TC/HDL-C ratio; eGFR (30 to 59 mL/min/1.73 m2)	Smoker	Age interaction term (Age × smoker); Age interaction term (Age × HbA1c); Age interaction term (Age × TC/HDL-C ratio)
Cardiovascular	Wan et al., 2018	Anti-hypertensive drugs used, OHA; Insulin drug	HbA1c; HbA1c2; TC/HDL-C ratio; ln(urine ACR + 1); eGFR (60 to 89 mL/min/1.73 m2); eGFR (30 to 59 mL/min/1.73 m2); eGFR (<30 mL/min/1.73 m2)	Smoker	Age interaction term (Age × TC/HDL-C ratio)
Cardiovascular	Williams 2020		blood urea nitrogen, blood albumin, hemoglobin A1c	Smoking history	
Cardiovascular	Williams 2020	Implatable cardioverter defribrillator	blood urea nitrogen, blood albumin, hemoglobin A1c	Smoking history	
Cardiovascular	Williams 2020	Pacemaker	blood urea nitrogen, blood albumin, hemoglobin A1c, Glucose, Chloride, Red blood cell count, Red cell distribution width	Smoking history	
Cardiovascular	Wan et al., 2018		HbA1c; HbA1c2; TC/HDL-C ratio; eGFR (30 to 59 mL/min/1.73 m2)	Smoker	Age interaction term (Age × TC/HDL-C ratio)
Cardiovascular	Yang et al., 2007		HbA1c, spot urine albumin-to-creatinine ratio (ACR)		
Cardiovascular	Yang et al., 2007		Hemoglobin A1C; Total-to-HDL cholesterol ratio	Smoking status	
Cardiovascular	Yang et al., 2008a		HbA1c, Log10 (ACR+1) and blood Hb at baseline		

Cardiovascular	Yang et al., 2008d				
Cardiovascular	Yang et al., 2008b		Log10(eGFR), Log10(1 spot urine ACR), Non–high-density lipoprotein cholesterol	Current smoker	
Cardiovascular	Yang et al., 2008b		Hemoglobin A1C; Ln(total cholesterol–high-density lipoprotein cholesterol ratio);	Smoking status	
Cardiovascular	Yeboah et al., 2014		log (CAC + 25)		
Cardiovascular	Yeboah et al., 2014				UKPDS score; Log (CAC þ 25)
Cardiovascular	Yang et al. 2020	Hypertension medication	triglycerides, hemoglobin A1c, serum creatinine		
Cardiovascular	Yu 2019		(Fasting glucose/10)2, (Fasting glucose/10)3, (e(high-density lipoprotein cholesterol)/10)−0.5, (e(high-density lipoprotein cholesterol)/10)−0.5×ln(e(high-density lipoprotein cholesterol)/10), {e[log10(Triglyceride)]}−0.5, {e[log10(Triglyceride)]}−0.5×ln{e[log10(Triglyceride)]}, Low-density lipoprotein cholesterol ≥2.60, International normalized ratio ≥0.86 or D-dimer ≥0.15 or fibrinogen ≥3.19 or thrombin time ≥14.8, Prothrombin time activity ≥128 or activated partial thromboplastin time ≥33.56 or prothrombin time ≥9.8, Thyroid-stimulating hormone ≥2.04 or free thyroxine ≥11.93 or free triiodothyronine ≥4.24, Magnesium ≥0.93 or phosphorus ≥1.23 or potassium ≥4.36 or sodium ≥141, HCO3 ≥23.6 or chlorine ≥102.3 or calcium ≥2.23, Total bilirubin ≥7.2 or total protein ≥63.4, Cholinesterase ≥6.85 or alanine transaminase ≥16 or		

			gamma-glutamyl transtransferase ≥23 or alkaline phosphatase ≥74, Direct bilirubin ≥3.4 or globulin ≥25.48 or indirect bilirubin ≥3.7, Urine-specific gravity ≥1.01 or 24 hours total urine protein ≥0.86 or urea ≥7.38, Basophil ≥0.03×109/L or eosinophil granulocyte ≥0.13×109/L or mean corpuscular hemoglobin ≥29.9 or platelet distribution width ≥16.75 or plateletcrit ≥0.169% or monocytes ≥7.5%, Lymphocyte ≥26.1% or neutrophil ≥63% or hemoglobin ≥117, Hematocrit ≥0.37 or red blood cell distribution width ≥13.6% or neutrophil ≥4.2×109/L or mean corpuscular hemoglobin concentration ≥329, Lymphocyte ≥1.7×109/L or mean corpuscular volume ≥91 or monocytes×109/ L≥0.5,	
Cardiovascular	Zethelius et al., 2011		Log of TC:HDL; Log of HbA1c;	Smoker
Cardiovascular	Zgibor et al., 2006		AIC; ln total cholesterol/HDL cholesterol	Smoking status
Cardiovascular	Zgibor et al., 2010		Higher white blood cell count, lower HDLc	
Kidney	Aminian et al., 2019	Triglycerides; Noninsulin diabetes medications; Insulin; Lipid-lowering medications; Renin-angiotensin system inhibitors; Other antihypertensive medications; Aspirin; Warfarin	HcA1c (%); eGFR; LDL	Smoking status
Kidney	Basu S., 2017	blood pressure-lowering drugs, oral diabetes drugs, anticoagulant use	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin:creatinine ratio	Smoking
Kidney	Basu S., 2017	blood pressure-lowering drugs, oral diabetes drugs, anticoagulant use	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine	Smoking

Kidney	Basu S et al., 2018	Current medication use: statin, oral diabetes medications including metformin, anticoagulants other than aspirin	HbA1c %, total cholesterol, HDL cholesterol, urine creatinine, urine microalbuminto- creatinine ratio	current tobacco smoking	
Kidney	Basu S et al., 2018		HbA1c %, HDL and LDL cholesterol, white blood cell count, estimated GFR (eGFR), Haemoglobin	current tobacco smoking,	
Kidney	Dagliati et al., 2018	Antihypertensive therapy	HBA1C	Smoking habit	
Kidney	Dorajoo et al., 2017		Baseline UACR, mean HbA1c (%), HbA1c-CV		
Kidney	Dunkler et al., 2015		UACR, eGFR		
Kidney	Dunkler et al., 2015	laser therapy for diabetic retinopathy, number of antihypertensive drugs prescribed	d-UACRtp, eGFR, glucose, fasting LDL		
Kidney	Elley et al., 2013		Serum creatinine		
Kidney	Elley et al., 2013		Serum creatinine, HbA1c		
Kidney	Elley et al., 2013		Serum creatinine, HbA1c		
Kidney	Miao et al., 2017		Creatinine, HDL cholesterol	Diet control or physical activity	
Kidney	Peters et al., 2017	Diuretic use	HDL cholesterol, apoA4, C1QB, CD5L, IBP3		
Kidney	Tanaka et al., 2013		HbA1c, ACR	Current smoker	
Kidney	Shao et al.,2018		HbA1c		
Kidney	Vergouwe et al., 2010		HbA1c, AER	Smoking	
Kidney	Wan, E. et al., 2017a	Anti-hypertensive drugs used; Oral drug; Insulin drug	HbA1c; HbA1c2; ln(Urine ACR + 1); eGFR (60-89 ml/min/1.73m2); eGFR (< 60 ml/min/1.73m2)	Smoker	Age*insulin; Age* ln(Urine ACR + 1)

Kidney	Wan, E. et al., 2017a	Anti-hypertensive drugs used; Oral drug; Insulin drug	HbA1c; HbA1c; ln(Urine ACR + 1); eGFR (>90 ml/min/1.73m2); eGFR (60-89 ml/min/1.73m2); eGFR (< 60 ml/min/1.73m2)		Age*eGFR(60-89 ml/min/1.73m2); Age*eGFR(< 60 ml/min/1.73m2)
Kidney	Yang et al., 2006		log10 TC:HDL-C ratio		
Kidney	Yang et al., 2006		Log10 ACR, eGFR, Haematocrit (per 0.1 l/l)		
Kidney	Yang et al., 2006	Adjusted number of months using ACEIs	eGFR; Haematocrit; Log10 ACR		
Mortality	Arnold et al., 2016	Currently on insulin	Admission creatinine, admission hemoglobin, fasting glucose	Not currently working, active during leizure time	in-hospital revascularization
Mortality	Aminian et al., 2019	Triglycérides; Noninsulin diabetes medications; Insulin; Lipid-lowering medications; Renin-angiotensin system inhibitors; Other antihypertensive medications; Aspirin; Warfarin	HbA1c (%); eGFR; LDL	Smoking status	
Mortality	Basu S et al., 2017	blood pressure-lowering drugs, statins, Anticoagulants	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio	Smoking	
Mortality	Basu et al., 2018	Current use of statin, oral diabetes medications including metformin, and anticoagulants other than aspirin	Total cholesterol, HDL cholesterol, urine creatinine, urine microalbuminto-creatinine ratio, and hemoglobin A1c	Current tobacco smoking	
Mortality	Berkelmans et al., 2019	insulin treatment	HbA1c, eGFR, non-HDL-c	Current smoking	
Mortality	Copetti 2019	antihypertensive and insulin therapy	low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, and albumin-to-creatinine ratio		
Mortality	Copetti 2019	antihypertensive and insulin therapy, anticoagulant therapy	low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein		

			cholesterol, and albumin-to-creatinine ratio, eGFR		
Mortality	Copetti 2019				
Mortality	De Cosmo et al., 2013	antihypertensive and insulin therapy	LDL, triglycerides, HDL, ACR levels		
Mortality	Li et al., 2018	Anti-diabetes medications	Variation of fasting plasma glucose (%); Variation of HbA1c (%); Creatinine (mg/dL); Total cholesterol to HDL ratio		Hospitalization status one year prior to baseline
Mortality	McEwen et al., 2012	use of a diuretic		Smoking	Charlson index
Mortality	McEwen et al., 2012	use of a diuretic or beta blocker, treatment with insulin with or without oral medication	LDL cholesterol	Smoking	Charlson index
Mortality	Robinson et al., 2015				
Mortality	Robinson et al., 2015		HbA1c (per 10 mmol/mol), HbA1c squared, Total/HDL cholesterol ratio	Smoker, Ex-smoker	
Mortality	Robinson et al., 2015		HbA1c (per 10 mmol/mol), HbA1c squared, Total/HDL cholesterol ratio, eGFR (per 10 mL/mim/1.73m2), eGFR squared	Smoker, Ex-smoker	
Mortality	Savonitto et al., 2018		NT-proBNP, HbA1c, haemoglobin		
Mortality	Shao et al., 2018		HbA1c, HbA1c^2	Smoking	
Mortality	Tanaka et al., 2013			Current smoker, Leizure time physical activity (LTPA)	
Mortality	van Diepen et al., 2014		serum albumin and hemoglobin level	Smoking status	Karnofsky scale
Mortality	Yang et al., 2008d	insulin use	blood hemoglobin levels, random spot urinary albumin-creatinine ratio, estimated glomerular filtration rate at enrollment		

Mortality	Yang et al., 2008d	insulin use	blood hemoglobin levels, random spot urinary albumin-creatinine ratio, estimated glomerular filtration rate at enrollment		
Mortality	Yang et al., 2008d	insulin use	blood hemoglobin levels, random spot urinary albumin-creatinine ratio, estimated glomerular filtration rate at enrollment		
Mortality	Yang et al., 2008d	insulin use	blood hemoglobin levels, random spot urinary albumin-creatinine ratio, estimated glomerular filtration rate at enrollment		
Mortality	Wan, E. et al., 2017b – model 1	Anti-hypertensive drugs usage; Insulin usage; Lipid-lowering agents usage	HbA1c; HbA1c2; ln (Urine ACR +1); eGFR (60 to 89 mL/min/1.73 m2); eGFR (30 to 59 mL/min/1.73 m2); eGFR (<30 mL/min/1.73 m2)	Smoker	Age*eGFR (60 to 89 mL/min/1.73 m2); Age*eGFR (30 to 59 mL/min/1.73 m2); Age*eGFR (<30 mL/min/1.73 m2)Age*(BMI + BMI2); Age*(SBP + SBP2)
Mortality	Wan, E. et al., 2017b – model 2	Anti-hypertensive drugs usage; Oral anti-diabetic drugs; Insulin usage; Lipid-lowering agents usage	HbA1c; HbA1c2; ln (Urine ACR +1); eGFR (60 to 89 mL/min/1.73 m2); eGFR (30 to 59 mL/min/1.73 m2); eGFR (<30 mL/min/1.73 m2)	Smoker	Age*eGFR (60 to 89 mL/min/1.73 m2); Age*eGFR (30 to 59 mL/min/1.73 m2); Age*eGFR (<30 mL/min/1.73 m2); Age*(HbA1c + HbA1c2); Age*(DBP + DBP2); Age*Lipid-lowering agents used

eyes	Basu S et al., 2017	blood pressure-lowering drugs, oral diabetes drugs	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine		
eyes	Basu S et al., 2017	blood pressure-lowering drugs, oral diabetes drugs	HbA1c %, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin:creatinine ratio		
eyes	Basu et al., 2018	Current use of statin, oral diabetes medications including metformin, and anticoagulants other than aspirin	Total cholesterol, HDL cholesterol, urine creatinine, urine microalbuminto-creatinine ratio, and hemoglobin A1c	Current tobacco smoking	
eyes	Basu et al., 2018		HbA1c, HDL and LDL cholesterol, estimated GFR (eGFR), white blood cell count. Haemoglobin	Current tobacco smoking	
eyes	Dagliati et al., 2018	Antihypertensive therapy	HBA1C	Smoking habit	
eyes	Garcia-Finana et al., 2019		HbA1c		Missing appointment at previous visit before prediction
eyes	Garcia-Finana et al., 2019		HbA1c		
eyes	Harrison et al., 2011a		mfERG implicit time		
eyes	Harrison et al., 2011b		mfERG amplitude (Amp) Z-score, Multifocal electroretinogram (mfERG) implicit time (IT) Z-score, SPB		
eyes	Kang 2018		HbA1c level		
eyes	Schreur 2019		HbA1c		
eyes	Shao 2018		HbA1c, LDL		
eyes	Tanaka et al., 2013		HbA1c, ACR		
Hypoglycemia	Chow 2018	intensive glycemic management, insulin, antihypertensive, HMG-CoA reductase inhibitors,	serum creatinine, and urinary albumin creatinine ratio		

		sulfonylurea, biguanide and meglitinide			
Hypoglycemia	Han 2018	insulin or multiple oral hypoglycemic agent (OHA) use	fasting glucose level	Current smoking, exercice, alcohol consumption	Charlson Comorbidity Index score
Hypoglycemia	Karter et al., 2017	Insulin use, sulfonylurea use			
Hypoglycemia	Li 2019	Antibiotics within 30 days, Insulin, SU within 12 months	Last HbA1c, Serum calcium (mg/dL), glomerular filtration rate	Alcohol	Last hospital discharge
Hypoglycemia	Mueller 2020	180 pharmacy variables	30 laboratory variables		68 procedure variables, 8 utilization variables.
Hypoglycemia	Schroeder et al., 2017	Insulin use; Metformin use; Number of classes of glucose lowering medication	A1c; eGFR		Hospitalization within the previous 365 days; Emergency department visit within the previous 365 days;
Hypoglycemia	Schroeder et al., 2017	Insulin use	hemoglobin A1c, eGFR		
Hypoglycemia	Shah 2019	insulin use, other oral agent use (nonhypoglycemia inducing)			
Hypoglycemia	Weiner 2020	insulin other than long-acting insulin, no antibiotics, antibiotics with a SU drug, long-acting insulin plus an SU within 90 days	A1C 6.5% or less, serum calcium	Alcohol	Medicaid
Nerve	Dagliati et al., 2018		HBA1c	Smoking habit	
Nerve	Basu et al., 2017	blood pressure-lowering drugs, oral diabetes drugs	HbA1c, total cholesterol, HDL cholesterol, Serum creatinine, Urine albumin: creatinine ratio		

Nerve	Basu et al., 2017	blood pressure-lowering drugs, oral diabetes drugs	HbA1c, total cholesterol, HDL cholesterol, Serum creatinine		
Nerve	Shao et al., 2018		HbA1c, LDL		
Cancer	Boursi et al., 2017	Anti-diabetic medications, proton pump inhibitors	Hemoglobin A1C, hemoglobin, total cholesterol, creatinine, and alkaline phosphatase	Smoking	
Cancer	Yang et al., 2008c		formula linear-transformed total cholesterol and WBC count	Current smoking	
Fracture	Martinez-Laguna 2018	ca+d use (calcium and vitamin D supplements)			
Fracture	Martinez-Laguna 2018	Statine use, ca+d use (calcium and vitamin D supplements)			
Cognitive problems	Exalto et al., 2013				
Other complications	Li et al., 2018	Anti-diabetes medications, Cardiovascular medications	HbA1c (%); Variation of fasting plasma glucose (%); Variation of HbA1c (%); Creatinine (mg/dL); Total cholesterol to HDL ratio		Hospitalization status one year prior to baseline
Other complications	Mueller et al., 2020	180 pharmacy variables	30 laboratory variables		68 procedure variables, 8 utilization variables.
Other complications	Selby et al., 2001	Antihypertensive, diabetes treatment	Serum creatinine, mean HbA1C, albuminuria, mean total cholesterol		primary care visits
Other complications	Selby et al., 2001	Diabetes treatment, Use of antilipemic medications	Mean HbA1c, Mean LDL cholesterol	Smoking status	Emergency department visit
Other complications	Selby et al., 2001	treatment of diabetes	serum creatinine		Nonmaternity hospitalizations, number of visits to specialists,
Other complications	Berkelmans et al., 2019	insulin treatment	HbA1c, eGFR, non-HDL-c	Current smoking	

Other complications	Soedamah-Muthu et al., 2014	HbA1c level, albumin/creatinine ratio and HDL-cholesterol level

Table 2: Condensed table of predictors included in selected models

	Age	Sex	Race or ethnicity	Blood pressure	Smoking	LDL**	BMI or waist circomference	Other lifestyle factors	Pre-existing health condition	Insulin	Lipid lowering medication	Renin-angiotensin system inhibitors	Other medication than insulin	HbA1C
Cardiovascular complications	70	59	26	87	85	81	30	46	68	24	16	4	44	72
Mortality	34	25	8	23	18	25	26	4	21	23	7	2	31	19
Kidney complications	23	21	19	23	24	22	25	2	24	4	8	2	22	30
Eyes complications	8	9	8	14	7	12	11	4	9	0	2	0	10	18
Hypoglycemia*	13	4	7	1	1	0	7	5	13	13	1	0	14	8
Nerve complication	4	5	5	4	3	5	3	0	5	0	0	0	4	8
Cancer	2	0	0	0	2	0	1	0	2	0	0	0	1	1
Fracture	2	2	0	0	0	0	0	0	2	0	1	0	2	0
Dementia	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Other complications	7	6	1	4	1	5	13	0	11	4	1	0	12	14

** Hypoglycemia include severe hypoglycemia; ** include all models that consider total cholesterol and HDL, total/cholesterol ratio, and non-HDL; ***One study with did not specify its 388 predictors and is not listed here for that reason*

LIST OF APPENDIX

DECLARATIONS

Ethics Approval, Consent to Participate and Consent for Publication

As this study will be based only on published studies, ethics approval is not required. The result will be published in a peer review journal.

Availability of Data and Materials

Data are available by requesting to the corresponding author

Authors' Contributions

HW originally conceptualized the study, which was then led by RN as principal investigator. RN, IF, closely contributed to the design of the study. Team members provided expertise in the definition of the search strategy for predictors (HW, DG, SS), in the definition of the search strategy for diabetes complications (HW, BS, CY, SS), in prediction models, and (RN, IF, GN, BS) in study selection and extraction (RN, GN, IN, SS, CY, HW). RN, IF, and GN collaborated to draft the grid for extraction data and do pilot screening. CRB, SC, CR and RN participated in data screening, selection and extraction. RN, CRB and GN drafted the first version of the article with early revision by HW. HW, DG, SD and CY prepared the dissemination plan. All the co-authors critically revised the article and approved the final version for submission for publication. RN and HW had full access to all the data and had final responsibility for the decision to submit for publication.

Acknowledgements

The authors gratefully acknowledge the contributions of Jimmy Chau, Carol-Ann Ferlatte, Jean Mardenli, Thierry Provencher, Yihong Yu, to this project as research assistants and staff, of information experts Frédéric Bergeron and William Witteman, for assistance with search strategy, screening and selection of articles for the systematic review, and of the many patient partners of the Diabetes Action Canada who contributed greatly to this research project as a whole but who were not able to accept the invitation to participate on this

particular paper as co-authors due to time constraints. We thank all authors of the original articles who generously gave their time to validate the data we had extracted from their papers. Finally, we thank all study participants for helping us identify ways to improve diabetes care.

Funding

Funding for this study comes from two grants from the Canadian Institutes of Health Research (CIHR) FDN-148426 (Foundation grant, PI: Witteman) and SCA-145101 (SPOR chronic disease network grant funding Diabetes Action Canada, PI: Lewis). The CIHR had no role in determining the study design, the plans for data collection or analysis, the decision to publish, nor the preparation of this manuscript. HW is funded by a Research Scholar Junior 2 Career Development Award by the Fonds de Recherche du Québec—Santé. RN received postdoctoral fellowship from Diabetes Action Canada and another from the Society for Medical Decision Making and the Gordon and Betty Moore Foundation.

Potential conflicts of interest

RN is funded by Diabetes Action Canada, a strategic patient oriented research (SPOR) network in diabetes and its related complications, part of the Canadian Institutes of Health Research (CIHR) SPOR Program in Chronic Disease. Patient partners were recruited through Diabetes Action Canada and some co-authors also collaborated with Diabetes Action Canada.

References

1. World Health Organization. *Global report on diabetes*. (2016).
2. International Diabetes Federation. *IDF Diabetes Atlas*. (2017).
3. Nickerson, H. D. & Dutta, S. Diabetic complications: current challenges and opportunities. *J. Cardiovasc. Transl. Res.* **5**, 375–379 (2012).
4. Kent, P., Cancelliere, C., Boyle, E., Cassidy, J. D. & Kongsted, A. A conceptual framework for prognostic research. *BMC Med. Res. Methodol.* **20**, 172 (2020).
5. Lagani, V., Koumakis, L., Chiarugi, F., Lakasing, E. & Tsamardinos, I. A systematic review of predictive risk models for diabetes complications based on large scale clinical studies. *J. Diabetes Complications* **27**, 407–413 (2013).
6. Lee, E. T. *et al.* Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. *Circulation* **113**, 2897–2905 (2006).
7. Siervo, M., Bunn, D., Prado, C. M. & Hooper, L. Accuracy of prediction equations for serum osmolarity in frail older people with and without diabetes. *Am. J. Clin. Nutr.* **100**, 867–876 (2014).
8. Huffman, F. G., Zarini, G. G., McNamara, E. & Nagarajan, A. The Healthy Eating Index and the Alternate Healthy Eating Index as predictors of 10-year CHD risk in Cuban Americans with and without type 2 diabetes. *Public Health Nutr.* **14**, 2006–2014 (2011).
9. van Dieren, S. *et al.* Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. *Heart* **98**, 360–369 (2012).
10. Harding, J. L., Pavkov, M. E., Magliano, D. J., Shaw, J. E. & Gregg, E. W. Global trends in diabetes complications: a review of current evidence. *Diabetologia* **62**, 3–16 (2019).
11. Rawshani, A. *et al.* Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* **379**, 633–644 (2018).
12. Peters, M. D. J. *et al.* Chapter 11: Scoping Reviews (2020 version). in *Joanna Briggs Institute Reviewer's Manual* (eds. Aromataris, E. & Munn, Z.) (JBI, 2020).
13. Levac, D., Colquhoun, H. & O'Brien, K. K. Scoping studies: advancing the methodology. *Implement. Sci.* **5**, 69 (2010).
14. Tricco, A. C. *et al.* PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* (2018) doi:10.7326/M18-0850.
15. Ndjaboue, R. *et al.* Predictive models of diabetes complications: protocol for a scoping review. *Systematic Reviews* **9**, 137 (2020).
16. Bergold, J. & Thomas, S. Participatory Research Methods: A Methodological Approach in Motion. *Forum Qual. Soc. Res.* **13**, (2012).
17. Diabetes Action Canada - SPOR Network. *SPOR Network* https://diabetesaction.ca/.
18. Dogba, M. J., Dipankui, M. T., Chipenda Dansokho, S., Légaré, F. & Witteman, H. O. Diabetes-related complications: Which research topics matter to diverse patients and caregivers? *Health Expect.* **21**, 549–559 (2018).
19. Brannick, B., Wynn, A. & Dagogo-Jack, S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. *Exp. Biol. Med.* **241**, 1323–1331 (2016).
20. Framingham Heart Study. https://www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/.
21. Haneuse, S. & Bartell, S. Designs for the combination of group- and individual-level data. *Epidemiology* **22**, 382–389 (2011).
22. Rothman, K. J., Greenland, S., Lash, T. L. & Others. Modern epidemiology. (2008).
23. Altman, D. G. & Royston, P. What do we mean by validating a prognostic model? *Stat. Med.* **19**, 453–473 (2000).
24. Steyerberg, E. W. *et al.* Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* **21**, 128–138 (2010).
25. Boggenpoel, B., Madasa, V., Jeftha, T. & Joseph, C. Systematic scoping review protocol for clinical prediction rules (CPRs) in the management of patients with spinal cord injuries. *BMJ Open* **9**, e025076 (2019).
26. Dewar, B. *et al.* Protocol for a systematic scoping review of reasons given to justify the performance of randomised controlled trials. *BMJ Open* **9**, e027575 (2019).

27. EndNote | Clarivate Analytics. *EndNote* https://endnote.com/.
28. Covidence systematic review software.
29. Moons, K. G. M. *et al.* Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med.* **11**, e1001744 (2014).
30. Arksey, H. & O'Malley, L. Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* **8**, 19–32 (2005).
31. Wolff, R. F. *et al.* PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann. Intern. Med.* **170**, 51–58 (2019).
32. Holmberg, L. & Vickers, A. Evaluation of prediction models for decision-making: beyond calibration and discrimination. *PLoS medicine* vol. 10 e1001491 (2013).
33. Colquhoun, H. L. *et al.* Scoping reviews: time for clarity in definition, methods, and reporting. *J. Clin. Epidemiol.* **67**, 1291–1294 (2014).
34. Stevens, R. J. & Poppe, K. K. Validation of clinical prediction models: what does the 'calibration slope' really measure? *J. Clin. Epidemiol.* **118**, 93–99 (2020).
35. Mueller, L. *et al.* Application of Machine Learning Models to Evaluate Hypoglycemia Risk in Type 2 Diabetes. *Diabetes Ther.* **11**, 681–699 (2020).
36. Wan, E. Y. F. *et al.* Development of a cardiovascular diseases risk prediction model and tools for C hinese patients with type 2 diabetes mellitus: A population-based retrospective cohort study. *Diabetes Obes. Metab.* **20**, 309–318 (2018).
37. Wan, E. Y. F. *et al.* Prediction of five-year all-cause mortality in Chinese patients with type 2 diabetes mellitus--A population-based retrospective cohort study. *J. Diabetes Complications* **31**, 939–944 (2017).
38. Wan, E. Y. F. *et al.* Prediction of new onset of end stage renal disease in Chinese patients with type 2 diabetes mellitus – a population-based retrospective cohort study. *BMC Nephrology* vol. 18 (2017).
39. Zgibor, J. C. *et al.* Development of a coronary heart disease risk prediction model for type 1 diabetes: the Pittsburgh CHD in Type 1 Diabetes Risk Model. *Diabetes Res. Clin. Pract.* **88**, 314–321 (2010).
40. Cederholm, J. *et al.* A new model for 5-year risk of cardiovascular disease in Type 1 diabetes; from the Swedish National Diabetes Register (NDR). *Diabet. Med.* **28**, 1213–1220 (2011).
41. Kang, E. Y.-C. *et al.* Nomogram for prediction of non-proliferative diabetic retinopathy in juvenile-onset type 1 diabetes: a cohort study in an Asian population. *Sci. Rep.* **8**, 12164 (2018).
42. Schreur, V. *et al.* Validation of a model for the prediction of retinopathy in persons with type 1 diabetes. *Br. J. Ophthalmol.* (2019).
43. Vistisen, D. *et al.* Prediction of First Cardiovascular Disease Event in Type 1 Diabetes Mellitus: The Steno Type 1 Risk Engine. *Circulation* **133**, 1058–1066 (2016).
44. Zgibor, J. C., Piatt, G. A., Ruppert, K., Orchard, T. J. & Roberts, M. S. Deficiencies of cardiovascular risk prediction models for type 1 diabetes. *Diabetes Care* **29**, 1860–1865 (2006).
45. Soedamah-Muthu, S. S. *et al.* Predicting major outcomes in type 1 diabetes: a model development and validation study. *Diabetologia* **57**, 2304–2314 (2014).
46. Vergouwe, Y. *et al.* Progression to microalbuminuria in type 1 diabetes: development and validation of a prediction rule. *Diabetologia* **53**, 254–262 (2010).
47. Basu, S., Sussman, J. B., Berkowitz, S. A., Hayward, R. A. & Yudkin, J. S. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. *The Lancet Diabetes & Endocrinology* vol. 5 788–798 (2017).
48. Basu, S. *et al.* Validation of Risk Equations for Complications of Type 2 Diabetes (RECODe) using individual participant data from diverse longitudinal cohorts in the US. *Diabetes Care* **41**, 586–595 (2018).
49. Berkelmans, G. F. N. *et al.* Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. *European Heart Journal* vol. 40 2899–2906 (2019).
50. Cederholm, J. *et al.* Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. *Diabetes Care* **31**, 2038–2043 (2008).

51. Christianson, T. J. H., Bryant, S. C., Weymiller, A. J., Smith, S. A. & Montori, V. M. A pen-and-paper coronary risk estimator for office use with patients with type 2 diabetes. *Mayo Clin. Proc.* **81**, 632–636 (2006).
52. Chow, L. S., Zmora, R., Ma, S., Seaquist, E. R. & Schreiner, P. J. Development of a model to predict 5-year risk of severe hypoglycemia in patients with type 2 diabetes. *BMJ Open Diabetes Res Care* **6**, e000527 (2018).
53. Colombo, M. *et al.* Apolipoprotein CIII and N-terminal prohormone b-type natriuretic peptide as independent predictors for cardiovascular disease in type 2 diabetes. *Atherosclerosis* **274**, 182–190 (2018).
54. Copetti, M. *et al.* Estimation of Mortality Risk in Type 2 Diabetic Patients (ENFORCE): An Inexpensive and Parsimonious Prediction Model. *J. Clin. Endocrinol. Metab.* **104**, 4900–4908 (2019).
55. Dagliati, A. *et al.* Machine Learning Methods to Predict Diabetes Complications. *J. Diabetes Sci. Technol.* **12**, 295–302 (2018).
56. De Cosmo, S. *et al.* Development and validation of a predicting model of all-cause mortality in patients with type 2 diabetes. *Diabetes Care* **36**, 2830–2835 (2013).
57. Dorajoo, S. R. *et al.* HbA1c variability in type 2 diabetes is associated with the occurrence of new-onset albuminuria within three years. *Diabetes Res. Clin. Pract.* **128**, 32–39 (2017).
58. Dunkler, D. *et al.* Risk Prediction for Early CKD in Type 2 Diabetes. *Clin. J. Am. Soc. Nephrol.* **10**, 1371–1379 (2015).
59. Exalto, L. G. *et al.* Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *The Lancet Diabetes & Endocrinology* **1**, 183–190 (2013).
60. Guzder, R. N., Gatling, W., Mullee, M. A., Mehta, R. L. & Byrne, C. D. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. *Diabet. Med.* **22**, 554–562 (2005).
61. Han, K. *et al.* Development and validation of a risk prediction model for severe hypoglycemia in adult patients with type 2 diabetes: a nationwide population-based cohort study. *Clin. Epidemiol.* **10**, 1545–1559 (2018).
62. Karter, A. J. *et al.* Development and Validation of a Tool to Identify Patients With Type 2 Diabetes at High Risk of Hypoglycemia-Related Emergency Department or Hospital Use. *JAMA Intern. Med.* **177**, 1461 (2017).
63. Kengne, A. P. *et al.* Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. *Eur. J. Cardiovasc. Prev. Rehabil.* **18**, 393–398 (2011).
64. Kothari, V. *et al.* UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* **33**, 1776–1781 (2002).
65. Lyu, J. *et al.* A potent risk model for predicting new-onset acute coronary syndrome in patients with type 2 diabetes mellitus in Northwest China. *Acta Diabetol.* **57**, 705–713 (2020).
66. Martínez-Laguna, D. *et al.* Fracture risk in type 2 diabetic patients: A clinical prediction tool based on a large population-based cohort. *PLoS One* **13**, e0203533 (2018).
67. McEwen, L. N. *et al.* Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care* **35**, 1301–1309 (2012).
68. Miao, D. D. *et al.* Development and Validation of a Model for Predicting Diabetic Nephropathy in Chinese People. *Biomed. Environ. Sci.* **30**, 106–112 (2017).
69. Peters, K. E. *et al.* Identification of Novel Circulating Biomarkers Predicting Rapid Decline in Renal Function in Type 2 Diabetes: The Fremantle Diabetes Study Phase II. *Diabetes Care* **40**, 1548–1555 (2017).
70. Pfister, R., Cairns, R., Erdmann, E. & Schneider, C. A. A clinical risk score for heart failure in patients with type 2 diabetes and macrovascular disease: an analysis of the PROactive study. *Int. J. Cardiol.* **162**, 112–116 (2013).
71. Piniés, J. A. *et al.* Development of a prediction model for fatal and non-fatal coronary heart disease and cardiovascular disease in patients with newly diagnosed type 2 diabetes mellitus: the Basque Country Prospective Complications and Mortality Study risk engine (BASCORE). *Diabetologia* **57**, 2324–2333 (2014).

72. Tanaka, S. *et al.* Predicting macro- and microvascular complications in type 2 diabetes: the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine. *Diabetes Care* **36**, 1193–1199 (2013).
73. Williams, B. A., Geba, D., Cordova, J. M. & Shetty, S. S. A risk prediction model for heart failure hospitalization in type 2 diabetes mellitus. *Clin. Cardiol.* **43**, 275–283 (2020).
74. Yang, X. L. *et al.* End-stage renal disease risk equations for Hong Kong Chinese patients with type 2 diabetes: Hong Kong Diabetes Registry. *Diabetologia* **49**, 2299–2308 (2006).
75. Yang, X. *et al.* Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. *Diabetes Care* **30**, 65–70 (2007).
76. Yeboah, J. *et al.* Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. *Atherosclerosis* **236**, 411–417 (2014).
77. Yu, D. *et al.* Derivation and external validation of a risk prediction algorithm to estimate future risk of cardiovascular death among patients with type 2 diabetes and incident diabetic nephropathy: prospective cohort study. *BMJ Open Diabetes Research & Care* vol. 7 e000735 (2019).
78. Zethelius, B. *et al.* A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Research and Clinical Practice* vol. 93 276–284 (2011).
79. Aminian, A. *et al.* Predicting 10-Year Risk of End-Organ Complications of Type 2 Diabetes With and Without Metabolic Surgery: A Machine Learning Approach. *Diabetes care* vol. 43 852–859 (2020).
80. Davis, W. A., Colagiuri, S. & Davis, T. M. E. Comparison of the Framingham and United Kingdom Prospective Diabetes Study cardiovascular risk equations in Australian patients with type 2 diabetes from the Fremantle Diabetes Study. *Med. J. Aust.* **191**, 47–48 (2009).
81. Davis, W. A., Knuiman, M. W. & Davis, T. M. E. An Australian cardiovascular risk equation for type 2 diabetes: the Fremantle Diabetes Study. *Intern. Med. J.* **40**, 286–292 (2010).
82. Elley, C. R., Robinson, E., Kenealy, T., Bramley, D. & Drury, P. L. Derivation and Validation of a New Cardiovascular Risk Score for People With Type 2 Diabetes: The New Zealand Diabetes Cohort Study. *Diabetes Care* vol. 33 1347–1352 (2010).
83. Elley, C. R. *et al.* Derivation and validation of a renal risk score for people with type 2 diabetes. *Diabetes Care* **36**, 3113–3120 (2013).
84. Li, T.-C. *et al.* Establishment and validation of a prediction model for ischemic stroke risks in patients with type 2 diabetes. *Diabetes Res. Clin. Pract.* **138**, 220–228 (2018).
85. Li, T.-C. *et al.* Development and validation of prediction models for the risks of diabetes-related hospitalization and in-hospital mortality in patients with type 2 diabetes. *Metabolism* **85**, 38–47 (2018).
86. Robinson, T. *et al.* New Zealand Diabetes Cohort Study cardiovascular risk score for people with Type 2 diabetes: validation in the PREDICT cohort. *J. Prim. Health Care* **4**, 181–188 (2012).
87. Robinson, T. E., Elley, C. R., Kenealy, T. & Drury, P. L. Development and validation of a predictive risk model for all-cause mortality in type 2 diabetes. *Diabetes Res. Clin. Pract.* **108**, 482–488 (2015).
88. Shao, H., Fonseca, V., Stoecker, C., Liu, S. & Shi, L. Correction to: Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). *Pharmacoeconomics* **37**, 1069 (2018).
89. Yang, X. *et al.* Development and validation of a risk score for hospitalization for heart failure in patients with Type 2 diabetes mellitus. *Cardiovasc. Diabetol.* **7**, 9 (2008).
90. Yang, X. *et al.* Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. *Am. J. Cardiol.* **101**, 596–601 (2008).
91. Yang, X. *et al.* Predicting values of lipids and white blood cell count for all-site cancer in type 2 diabetes. *Endocr. Relat. Cancer* **15**, 597–607 (2008).
92. Yang, X. *et al.* Development and Validation of an All-Cause Mortality Risk Score in Type 2

Diabetes: The Hong Kong Diabetes Registry. *Arch. Intern. Med.* **168**, 451–457 (2008).
93. Yang, P., Zhao, Y. & Wong, N. D. Development of a Risk Score for Atrial Fibrillation in Adults with Diabetes Mellitus (from the ACCORD Study). *Arhythmias and conduction Disturbances* (2020).
94. Looker, H. C. *et al.* Protein biomarkers for the prediction of cardiovascular disease in type 2 diabetes. *Diabetologia* **58**, 1363–1371 (2015).
95. Savonitto, S. *et al.* Predictors of mortality in hospital survivors with type 2 diabetes mellitus and acute coronary syndromes. *Diab. Vasc. Dis. Res.* **15**, 14–23 (2018).
96. Stevens, R. J., Kothari, V., Adler, A. I., Stratton, I. M. & United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin. Sci.* **101**, 671–679 (2001).
97. García-Fiñana, M. *et al.* Personalized risk-based screening for diabetic retinopathy: A multivariate approach versus the use of stratification rules. *Diabetes Obes. Metab.* **21**, 560–568 (2019).
98. Harrison, W. W. *et al.* Prediction, by retinal location, of the onset of diabetic edema in patients with nonproliferative diabetic retinopathy. *Invest. Ophthalmol. Vis. Sci.* **52**, 6825–6831 (2011).
99. Harrison, W. W. *et al.* Multifocal electroretinograms predict onset of diabetic retinopathy in adult patients with diabetes. *Invest. Ophthalmol. Vis. Sci.* **52**, 772–777 (2011).
100. Hippisley-Cox, J. & Coupland, C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. *BMJ Open* **5**, e008503 (2015).
101. Schroeder, E. B. *et al.* Predicting the 6-month risk of severe hypoglycemia among adults with diabetes: Development and external validation of a prediction model. *J. Diabetes Complications* **31**, 1158–1163 (2017).
102. Selby, J. V., Karter, A. J., Ackerson, L. M., Ferrara, A. & Liu, J. Developing a prediction rule from automated clinical databases to identify high-risk patients in a large population with diabetes. *Diabetes Care* **24**, 1547–1555 (2001).
103. Weiner, M. *et al.* A randomized study on the usefulness of an electronic outpatient hypoglycemia risk calculator for clinicians of patients with diabetes in a safety-net institution. *Curr. Med. Res. Opin.* **36**, 583–593 (2020).
104. Li, X. *et al.* Predictive modeling of hypoglycemia for clinical decision support in evaluating outpatients with diabetes mellitus. *Curr. Med. Res. Opin.* **35**, 1885–1891 (2019).
105. Mukamal, K. J. *et al.* Prediction and classification of cardiovascular disease risk in older adults with diabetes. *Diabetologia* **56**, 275–283 (2013).
106. van Diepen, M. *et al.* Predicting mortality in patients with diabetes starting dialysis. *PLoS One* **9**, e89744 (2014).
107. Shah, B. R., Walji, S., Kiss, A., James, J. E. & Lowe, J. M. Derivation and Validation of a Risk-Prediction Tool for Hypoglycemia in Hospitalized Adults With Diabetes: The Hypoglycemia During Hospitalization (HyDHo) Score. *Can J Diabetes* **43**, 278–282.e1 (2019).
108. Qintar, M. *et al.* Individualizing Revascularization Strategy for Diabetic Patients With Multivessel Coronary Disease. *J. Am. Coll. Cardiol.* **74**, 2074–2084 (2019).
109. Arnold, S. V. *et al.* Predicting Adverse Outcomes After Myocardial Infarction Among Patients With Diabetes Mellitus. *Circ. Cardiovasc. Qual. Outcomes* **9**, 372–379 (2016).
110. Donnan, P. T., Donnelly, L., New, J. P. & Morris, A. D. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. *Diabetes Care* **29**, 1231–1236 (2006).
111. Boursi, B. *et al.* A Clinical Prediction Model to Assess Risk for Pancreatic Cancer Among Patients With New-Onset Diabetes. *Gastroenterology* **152**, 840–850.e3 (2017).
112. Garcia-Carretero, R., Vigil-Medina, L., Barquero-Perez, O. & Ramos-Lopez, J. Pulse Wave Velocity and Machine Learning to Predict Cardiovascular Outcomes in Prediabetic and Diabetic Populations. *J. Med. Syst.* **44**, 16 (2019).
113. World Health Organization. WHO | About cardiovascular diseases. https://www.who.int/cardiovascular_diseases/about_cvd/en/ (2011).
114. Dunlay, S. M. *et al.* Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From

the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* **140**, e294–e324 (2019).
115. Bloomfield, H. E. *et al.* Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes – A Systematic Review of the Evidence. *Search Publications - VA HSRD - Veterans Affairs* (2012).
116. Iqbal, Z. *et al.* Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy. *Clin. Ther.* **40**, 828–849 (2018).
117. Wright, A. K. *et al.* Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes: A Population-Based Cohort Study Quantifying Relationships in Ethnic Subgroups. *Diabetes Care* **40**, 338–345 (2017).
118. Pham, T. B. *et al.* Effects of Diabetic Complications on Health-Related Quality of Life Impairment in Vietnamese Patients with Type 2 Diabetes. *J Diabetes Res* **2020**, 4360804 (2020).
119. Rees, G. *et al.* Association Between Diabetes-Related Eye Complications and Symptoms of Anxiety and Depression. *JAMA Ophthalmol.* **134**, 1007–1014 (2016).
120. Wong, T. Y. & Sabanayagam, C. Strategies to Tackle the Global Burden of Diabetic Retinopathy: From Epidemiology to Artificial Intelligence. *Ophthalmologica* **243**, 9–20 (2020).
121. Kramer, C. K., Rodrigues, T. C., Canani, L. H., Gross, J. L. & Azevedo, M. J. Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies. *Diabetes Care* **34**, 1238–1244 (2011).
122. Boulton, A. J. M., Vileikyte, L., Ragnarson-Tennvall, G. & Apelqvist, J. The global burden of diabetic foot disease. *Lancet* **366**, 1719–1724 (2005).
123. Diabetes Canada Clinical Practice Guidelines Expert Committee *et al.* Diabetes and Mental Health. *Can J Diabetes* **42 Suppl 1**, S130–S141 (2018).
124. Glastras, S. J., Mohsin, F. & Donaghue, K. C. Complications of diabetes mellitus in childhood. *Pediatr. Clin. North Am.* **52**, 1735–1753 (2005).
125. Dabelea, D. *et al.* Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. *JAMA* **317**, 825–835 (2017).
126. Nanayakkara, N. *et al.* Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses. *Diabetologia* **64**, 275–287 (2021).
127. St Jean, BL. Information behavior of people diagnosed with a chronic serious health condition: a longitudinal study. (The University of Michigan, 2012).
128. Biernatzki, L. *et al.* Information needs in people with diabetes mellitus: a systematic review. *Syst. Rev.* **7**, 27 (2018).
129. Navar, A. M., Stone, N. J. & Martin, S. S. What to say and how to say it: effective communication for cardiovascular disease prevention. *Curr. Opin. Cardiol.* **31**, 537–544 (2016).
130. Ndjaboue, R. *et al.* Patients' perspectives on how to improve diabetes self-management and medical care: a qualitative study. *BMJ Open* **10**, e032762. (2020).
131. The Hormone Foundation. *Diabetes Caregivers Needs Assessment Survey – Executive Summary*. https://www.caregiving.org/wp-content/uploads/2020/05/NAC_Diabetes-Caregivers-Needs-Assessment-Survey_Executive-Summary-3-25-10_Final.pdf (2010).
132. Stol, D. M. *et al.* Mismatch between self-perceived and calculated cardiometabolic disease risk among participants in a prevention program for cardiometabolic disease: a cross-sectional study. *BMC Public Health* **20**, 740 (2020).
133. Rouyard, T., Kent, S., Baskerville, R., Leal, J. & Gray, A. Perceptions of risks for diabetes-related complications in Type 2 diabetes populations: a systematic review. *Diabet. Med.* **34**, 467–477 (2017).
134. Ivers, N. M. *et al.* Diabetes Canada 2018 clinical practice guidelines: Key messages for family physicians caring for patients living with type 2 diabetes. *Can. Fam. Physician* **65**, 14–24 (2019).
135. Fisher, L. *et al.* Understanding the sources of diabetes distress in adults with type 1 diabetes. *J. Diabetes Complications* **29**, 572–577 (2015).
136. Koumakis, L., Chiarugi, F., Lagani, V., Kouroubali, A. & Tsamardinos, I. Risk Assessment

Models for Diabetes Complications: A Survey of Available Online Tools. in *International Conference on Wireless Mobile Communication and Healthcare* 46–53 (2012).
137. Ferrari, S. L. *et al.* Diagnosis and management of bone fragility in diabetes: an emerging challenge. *Osteoporos. Int.* **29**, 2585–2596 (2018).
138. Yau, J. W. Y. *et al.* Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* **35**, 556–564 (2012).
139. Hemmingsen, B. *et al.* Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* **343**, d6898 (2011).
140. Gale, R. *et al.* Action on diabetic macular oedema: achieving optimal patient management in treating visual impairment due to diabetic eye disease. *Eye* **31**, S1–S20 (2017).
141. Fox, C. S. *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* **380**, 1662–1673 (2012).
142. Tatulashvili, S. *et al.* Socioeconomic inequalities and type 2 diabetes complications: A systematic review. *Diabetes Metab.* **46**, 89–99 (2020).
143. Ohkuma, T., Peters, S. A. E. & Woodward, M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. *Diabetologia* **61**, 2140–2154 (2018).
144. de Ritter, R. *et al.* Sex differences in the risk of vascular disease associated with diabetes. *Biol. Sex Differ.* **11**, 1 (2020).
145. Hendriksen, J. M. T., Geersing, G. J., Moons, K. G. M. & de Groot, J. A. H. Diagnostic and prognostic prediction models. *J. Thromb. Haemost.* **11 Suppl 1**, 129–141 (2013).
146. Spanakis, E. K. & Golden, S. H. Race/Ethnic Difference in Diabetes and Diabetic Complications. *Curr Diab Rep* **13**, (2013).
147. Diabetes in Canada. *Diabetes Canada* https://www.diabetes.ca/DiabetesCanadaWebsite/media/About-Diabetes/Diabetes%20Charter/2019-Backgrounder-Canada.pdf.
148. Statistics About Diabetes. *American Diabetes Association* http://www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.ca/
149. Center for Disease Control and Prevention. Diabetes Quick Facts. https://www.cdc.gov/diabetes/basics/quick-facts.html (2020).
150. Pencina, M. J., Goldstein, B. A. & D'Agostino, R. B. Prediction Models - Development, Evaluation, and Clinical Application. *N Engl J Med* **382**, 1583–1586 (2020).
151. Vandenbroucke, J. P. Observational research, randomised trials, and two views of medical science. *PLoS Med.* **5**, e67 (2008).
152. Cahan, E. M., Hernandez-Boussard, T., Thadaney-Israni, S. & Rubin, D. L. Putting the data before the algorithm in big data addressing personalized healthcare. *NPJ Digit Med* **2**, 78 (2019).
153. Sajin, S. Preventing Machine Learning Bias. *Medium* https://towardsdatascience.com/preventing-machine-learning-bias-d01adfe9f1fa (2018).
154. Dastin, J. Amazon scraps secret AI recruiting tool that showed bias against women. *Reuters* (2018).
155. Spitzer, W. O. Meta-meta-analysis: unanswered questions about aggregating data. *Journal of clinical epidemiology* vol. 44 103–107 (1991).
156. Abbasi, A. *et al.* Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. *BMJ* **345**, e5900 (2012).
157. Zidek, J. V., Wong, H., Le, N. D. & Burnett, R. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics* **7**, 441–451 (1996).
158. Yoo, W. *et al.* A Study of Effects of MultiCollinearity in the Multivariable Analysis. *Int J Appl Sci Technol* **4**, 9–19 (2014).
159. Vickers, A. J. & Elkin, E. B. Decision curve analysis: a novel method for evaluating prediction models. *Med. Decis. Making* **26**, 565–574 (2006).