# POWER2DM

**"Predictive model-based decision support for diabetes patient empowerment"**

**Research and Innovation Project**
**PHC 28 – 2015: Self-management of health and disease and decision support systems based on predictive computer modelling used by the patient him or herself**

# POWER2DM D2.2

# D2.2.1. Mid- and Long-term Predictive Component

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|---|---|
| *Due Date:* | 30th November 2016 (M10) |
| *Actual Submission Date:* | Jan 2016 (M12) |
| *Project Dates:* | Project Start Date: February 01, 2016<br>Project End Date: July 31, 2019<br>Project Duration: 42 months |
| *Deliverable Leader:* | TNO |

| **Project co-funded by the European Commission within H2020 Programme (20015-2016)** | | |
|---|---|---|
| **Dissemination Level** | | |
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**Document History:**

| Version | Date | Changes | From | Review |
|---|---|---|---|---|
| V1.0 | 29.11.2016 | Final version | TNO | SAS |
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# POWER2DM Consortium Partners

| Abbv | Participant Organization Name | Country |
|---|---|---|
| TNO | Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek | Netherlands |
| IDK | Institute of Diabetes "Gerhardt Katsch" Karlsburg | Germany |
| SRDC | SRDC Yazilim Arastirma ve Gelistirme ve Danismanlik Ticaret Limited Sirketi | Turkey |
| LUMC | Leiden University Medical Center | Netherlands |
| SAS | SAS Servicio Andaluz de Salud | Spain |
| SRFG | Salzburg Research Forschungs Gesellschaft | Austria |
| PD | PrimeData | Netherlands |
| iHealth | iHealth EU | France |

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# 1 Introduction

The primary goal of WP2 is to develop innovative programs, modules, and tools for short-term (Task 2.1) and long-term (Task 2.2) risk detection and risk prevention (Task 2.3) in personalized diabetes care and management by supporting patients efficiently in diabetes home monitoring and diabetes home care with patient-centered, real time decision support systems (DSS) which can finally be implemented into mobile-phone-based self-management equipments (Task 2.4). This deliverable reports on Task 2.2.

## 1.1 Purpose and Scope

The purpose of Task 2.2 Calibration of Medium-to-Long-term Predictive Models: MT2D-Marvel and Risk Scores – TNO(12), iHealth(1) (M3-M20), is to:

a· Define input/output of the M2TD-Marvel and Risk Scoring models for a real time, patient-centred predictive DSS module (TNO)

b· Generate a personalized home monitoring module based on self-monitoring data (TNO, iHealth)

c· Generate a personalized risk stratification module (TNO)

d· Validate that data quality from the pilot settings meets standards to properly drive the MT2D-Marvel and Risk Scoring models for the intended functionalities in the POWER2DM SMSS (TNO)

In the past period, work concentrated on subtask a.
Work on the remaining subtasks , b. – d. will be performed in the upcoming period (M11-20)

## 1.2 Reference Documents

- POWER2DM Description of Work (Proposal)
- D1.1 User Requirements and Use Case Scenarios
- D1.2 Requirements Specification of the POWER2DM Architecture
- D1.3 Conceptual Design of the POWER2DM Architecture
- D2.5 Mockups for GUI Components
- MISSION-T2D deliverable 4.2 Report on MF-HOMA model (weeks-months' time scale) http://www.mission-t2d.eu/MISSION-T2D/ewExternalFiles/MISSION-T2D_D4.2.pdf
- Section 2.3 in MISSION-T2D deliverable 4.4 Validation and refinement of the models in the overall workflow, http://www.mission-t2d.eu/MISSION-T2D/ewExternalFiles/MISSION-T2D_D4.4.pdf
- UKPDS Outcomes Model User Manual: https://www.dtu.ox.ac.uk/outcomesmodel/OM2Manual.pdf

## 1.3 Definitions and Acronyms

**Table 1 List of Abbreviations and Acronyms**

| Abbreviation/ Acronym | DEFINITION |
|---|---|
| CGM | Continuous glucose measurement |
| SMBG | Self-monitoring blood glucose |
| GUI | Graphical User Interface |
| UKPDS | United Kingdom Prospective Diabetes Study |
| T1D | Type 1 Diabetes |
| OM | Outcome Model |
| BG | Blood glucose |
| SDM | POWER2DM Shared Decision Making Application |
| CVD | Cardiovascular Disease |
| SMSS | POWER2DM Self-Management Support System |

# 2 Mid-term prediction models

## 2.1 Introduction

Health care is shifting towards personalized health and patient/citizen empowerment. There is a great need for tools that provide personally relevant health awareness and motivate behavior change. Forecasting models showing anticipated changes in health parameters over time, based on the current health status and different behavior scenarios, can provide such health awareness. These models are only relevant when both individual health parameters as well as environmental variables are incorporated. Whereas the KADIS model does so for the short term (i.e., days), the MT2D-Marvel model is such a novel multi-domain type 2 diabetes (T2D) forecasting model intended for an intermediate timescale (months-years).

## 2.2 MT2D-Marvel model

### 2.2.1 Background

The development of the MT2D-Marvel model within FP7 project MISSION-T2D (www.mission-t2d.eu) is described in MISSION-T2D deliverable 4.2 (see Reference Documents). Briefly, a systems dynamics approach was chosen for constructing a multi-domain T2D forecasting model. One of the challenges was to include fuzzy human factors into this model such as chronic stress, gut health and food quality which are not always easy to quantify (Morris 2010). Differential equation models involving such variables are very hard to construct due to this fuzziness of the variables and due to the lack of detailed dynamic data of the processes involved. A suitable semi-quantitative technique to approach this problem is the causal loop diagram (Homer 2006, Wang 2013). TNO has developed the software tool MARVEL (Method to Analyze Relations between Variables using Enriched Loops) to build enriched versions of causal loop diagrams in which the strength and speed of relationships can be categorically quantified (Zijderveld 2007). This simple method of quantification allows fast model simulations, resulting in projections of variables changes over time based on the start settings and control variable setting (Veldhuis 2015).

MARVEL was used to implement the main known causal mechanisms of T2D development involving different types of variables such as BMI, food intake, physical activity, chronic stress, fasting glucose levels, inflammation, and tissue damage, together establishing a multi-domain forecasting network model. The resulting T2D forecasting model was calibrated with literature data and qualitatively validated during MISSION-T2D using Whitehall II cohort study results. Whitehall II is a longitudinal cohort study of 10.308 civil servants working in London, included at the age of 35-55 years in 1985-88 (Marmot and Brunner 2005).
The original aim of the Whitehall II study was to investigate social and occupational influences on health and illness. 505 new diabetes cases were reported after 8.2 years of follow-up based on oral glucose tolerance tests. Several markers for glucose metabolism were measured such as fasting glucose, HbA1c, insulin sensitivity and beta-cell function.
The resulting T2D forecasting model consists of three groups of variables, one group related to energy balance, one to glucose metabolism, and one to other domains of health. Model simulations of various overeating scenarios produced outcome time trajectories for insulin sensitivity, beta cell function and blood glucose that were qualitatively similar to literature findings. The model qualitatively reproduces the compensation of rising insulin resistance by an increase of beta cell function (constant Disposition Index). Furthermore, the model qualitatively reproduces the well-known reinforcing loop wherein fasting glucose levels, once exceeding a toxicity threshold, lead to progressive damage to the pancreas thereby causing an even further increase of fasting glucose levels.
Data from the Whitehall II cohort for quantitative model validation became available only in the final phase of MISSION-T2D. The fact that data from only 2 out of 9 phases was made available for the

project posed a significant challenge for model validation and further analysis. Time course analysis e.g. using curve fitting procedures was not feasible. Analysis using Structural Equation Modelling was only partially successful as detailed in Section 2.3 in MISSION-T2D deliverable 4.4 (see Reference Documents). MISSION-T2D ended April 30, 2016 without finalizing the validation.
Work performed so far in POWER2DM included:

- Specification of model inputs and outputs for the purpose of POWER2DM
- Definition of the use cases for the MT2D-Marvel model
- Progression of the model calibration/validation
- Preparation for model adaptations for diabetes patients: type-1 diabetes, and medication use.

Progress within these subtasks, including examples of screenshots of implementation of the MT2D-Marvel prediction service on a server at TNO, is described below.

### 2.2.2 Specification of MT2D-Marvel model Inputs and Outputs:

Input and output of the MT2D-Marvel model are as specified in Table 1.

**Table 1. I/O specifications of the MT2D-Marvel model in POWER2DM.**

| MT2D-Marvel model | Unit | Valid range | Comment |
|---|---|---|---|
| **Model inputs** | | | |
| **Physical activity*** | kcal/day | 0-8000 | From activity tracker or questionnaire |
| **Food intake*** | kcal/day | 0-8000 | Calculate from body weight, height, sex and age and physical activity using Mifflin-St Jeor equation |
| **Fibre intake*** | g/day | 0-100 | From questionnaire or FatSecret app |
| **Sleep quality score** | | 0-10 | From questionnaire or sensor |
| **Model neutral variables** | | | |
| **BMI** | kg/m2 | 15-50 | |
| **Gut health*** | | | No measure commonly available |
| **Total cholesterol( TC)** | mmol/l | 1-15 | |
| **HDL-cholesterol** | mmol/l | less than TC | |
| **Triglycerides** | mmol/l | 0-30 | |
| **Systolic BP** | mmHg | 60-300 | |
| **Chronic stress score** | | 0-10 | Evaluated from questionnaires |
| **Inflammation (CRP**)** | mg/l | 0-500 | Maximized to 10 mg/l |
| **Fasting insulin** | pmol/l | 0-3000 | |
| **Model outputs** | | | |
| **Fasting glucose** | mmol/l | 0-50 | |
| **HOMA2-Insulin sensitivity ***** | % | 0-300 | |

* measure included in original MT2D-Marvel model but not in dynamic Bayesian network
** CRP shows too high variability in Whitehall data for use in practice. IL-1 RA was used instead in the dynamic Bayesian model but is not available in a clinical setting
*** not yet implemented

### 2.2.3 Definition of MT2D-Marvel model use cases in POWER2DM

In line with D1.1 and D1.2, the following use cases are currently implemented:

- UC4.1 - Analyze MT2D-MARVEL predictions with the existing patient context
- UC4.3 - Analyze outcome expectancies with MT2D-Marvel in case goals are reached

Re. UC 4.1, current patient data (see Table 1) are fed into the model and the model will return the expected values for plasma fasting glucose and insulin sensitivity in 5.7 years from now (5.7 years is the time interval between Whitehall II cohort Phase S3 and Phase S5 from which data were used for model calibration and validation. This prediction period may be shortened in which case a simple linear interpolation will be done).
Re. UC 4.3, a target value for plasma fasting glucose at the end of a specific prediction period time range (e.g. 6 years) can be fed into the model and the model will return the required changes in BMI, stress and sleep quality that are necessary to attain that target glucose value. The required change in BMI in parallel is translated into a required modification of calorie intake (using estimation from the Mifflin-St Jeor model).

### 2.2.4 Progression of the MT2D-Marvel model calibration/validation

Figure 1 shows a visual representation in the TNO-proprietary software MARVEL of the MT2D-Marvel model causal loop network structure from MISSION-T2D.

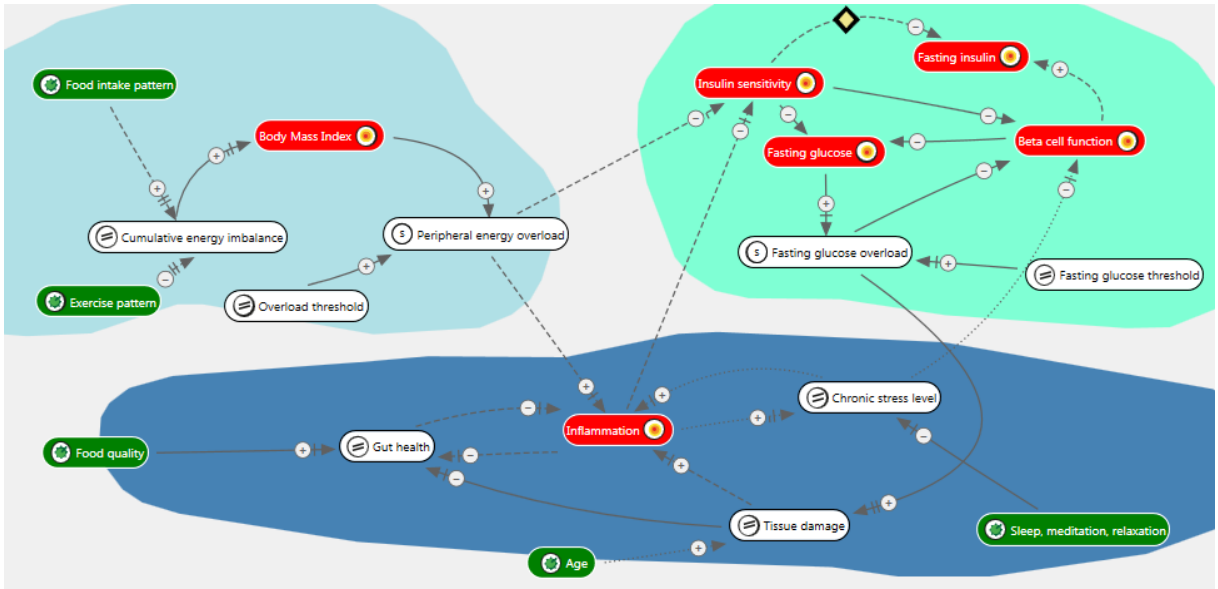


*Figure 1. Screenshot of MT2D-Marvel model developed in MISSION-T2D showing variables and causal interactions.Light blue cloud, energy domain; green cloud, diabetes domain; dark blue cloud, health domain.*

Work on model calibration/validation with the Whitehall II cohort data in MISSION-T2D using SEM (Structural Equation Modelling) showed that whereas the interactions in the energy and diabetes domains (cf. figure 1) could be accurately determined, this was not the case for the health domain. Specifically, the model was limited in explaining the observed variance in this domain. Table 2 shows illustrative results for one of the final results of MISSION-T2D.

**Table 2. Final result of MT2D-model calibration/validation in EU-FP7 MISSION-T2D: performance of SEM model using Bayesian estimation, informative priors, listwise deletion and only directly observed variables. St. regr. coeff = Standardized regression coefficient. Statistically significant predictors printed in bold. Clusters with low explained variance are printed in red.**

| | | | St. regr. coeff | Standard error | Explained variance | Standard error |
|---|---|---|---|---|---|---|
| **Diabetes** | | | | | | |
| | Fasting Insulin predicted by | | | | 0.74 | 0.02 |
| | | **Betacell function** | **0.62** | **0.02** | | |
| | | **Insulin sensitivity** | **-0.34** | **0.02** | | |
| | | | | | | |
| | Insulin sensitivity predicted by | | | | 0.05 | 0.01 |
| | | Inflamation | -0.06 | 0.03 | | |
| | | **BMI overload** | **-0.20** | **0.03** | | |
| | | | | | | |
| | Betacell function predicted by | | | | 0.46 | 0.02 |
| | | **Insulin sensitivity** | **-0.65** | **0.02** | | |
| | | **Glucose overload** | **-0.12** | **0.03** | | |
| | | Chronic stress | -0.01 | 0.02 | | |
| | | | | | | |
| | Fasting glucose predicted by | | | | 0.48 | 0.02 |
| | | **Betacell function** | **-0.74** | **0.03** | | |
| | | **Insulin sensitivity** | **-0.80** | **0.03** | | |
| | | | | | | |
| | Glucose overload predicted by | | | | 0.24 | 0.03 |
| | | Fasting glucose | 0.43 | 0.02 | | |
| | | | | | | |
| **Health** | Inflammation predicted by | | | | 0.02 | 0.01 |
| | | Chronic stress | -0.02 | 0.03 | | |
| | | Tissue damage | -0.07 | 0.03 | | |
| | | Food quality | 0.00 | 0.03 | | |
| | | **BMI overload** | **0.12** | **0.03** | | |
| | | | | | | |
| | Chronic stress predicted by | | | | 0.16 | 0.02 |
| | | **Sleep** | **-0.40** | **0.03** | | |
| | | | | | | |
| | Tissue damage predicted by | | | | 0.02 | 0.01 |
| | | Glucose overload | 0.00 | 0.03 | | |
| | | **Age** | **-0.11** | **0.03** | | |
| | | | | | | |
| **Energy** | BMI predicted by | | | | 0.01 | 0.01 |
| | | Food intake | 0.06 | 0.03 | | |
| | | Exercise | -0.05 | 0.03 | | |
| | | | | | | |
| | BMI overload predicted by | | | | 0.71 | 0.02 |
| | | BMI | 0.84 | 0.01 | | |

Based on this result, the modelling approach was critically assessed in Task 2.2. of POWER2DM during the past period. Investigations showed the following problems: 1) the effect sizes (strengths) of interactions in the model depended strongly on the value of model output variables (e.g., fasting glucose values) whereas the original model assumed constant effect sizes; 2)significant correlations were found between variables that were unconnected in the original model (e.g., chronic stress and beta cell function).
Therefore, it was decided to re-formulate the model as a dynamic Bayesian network with interactions only between those variables that showed a strong correlation. The network based on the observed correlations was implemented in the software Netica from Norsys Software Corporation (https://www.norsys.com/netica.html). Built-in Netica routines were used for sub-dividing the variable ranges into bins (i.e. intervals) and calculation of the initial, and conditional probabilities from the Whitehall II dataset. The classification (binning) of some variables was manually pruned to get better resolution especially in the ranges of higher glucose, thereafter the probability distributions were recalculated. The model structure is shown in figure 2.

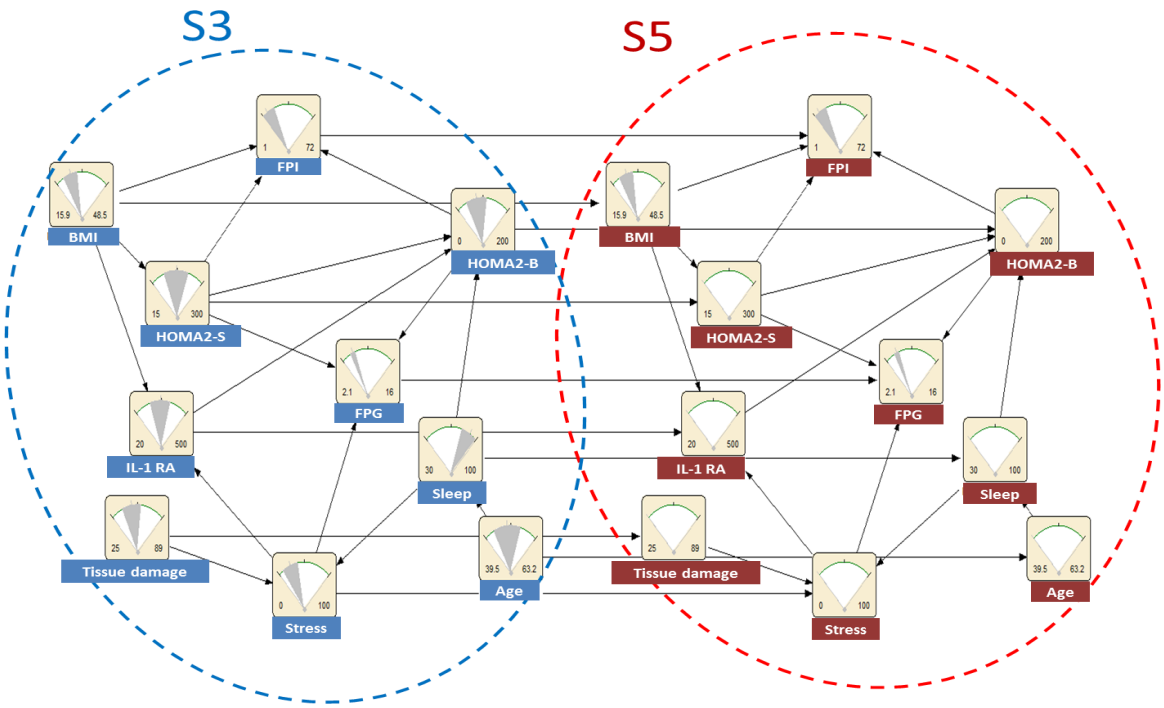


*Figure 2. Structure of the MT2D-Marvel model dynamic Bayesian network developed for POWER2DM derived from data distribution probabilities for two phases S3 and S5 of the Whitehall II cohort. FPI, fasting plasma insulin, FPG, fasting plasma glucose; IL-1 RA, Interleukin-1 receptor antagonist (inflammation marker); Tissue damage, construct of plasma cholesterol, plasma TG, and blood pressure values.*

Given a patient's current settings of model variables (see Table 1) as inputs, the software will calculate the expected values (value and standard deviation) of the output variables based on the conditional probability distributions in the dynamic Bayesian network. These values are the predictions of the MT2D-Marvel model output variables at a specified prediction interval (default: 6 years). Only a selection of these variables decided upon in Workpackage 1 will be shown to the physician and the patient. This corresponds to POWER2DM use case UC4.1 - Analyze MT2D-MARVEL predictions with the existing patient context.
Figure 3 shows a screenshot of the current implementation of the MT2D-Marvel prediction service on the Diamonds3 webserver at TNO (https://diamonds.tno.nl/diamonds3develop/).

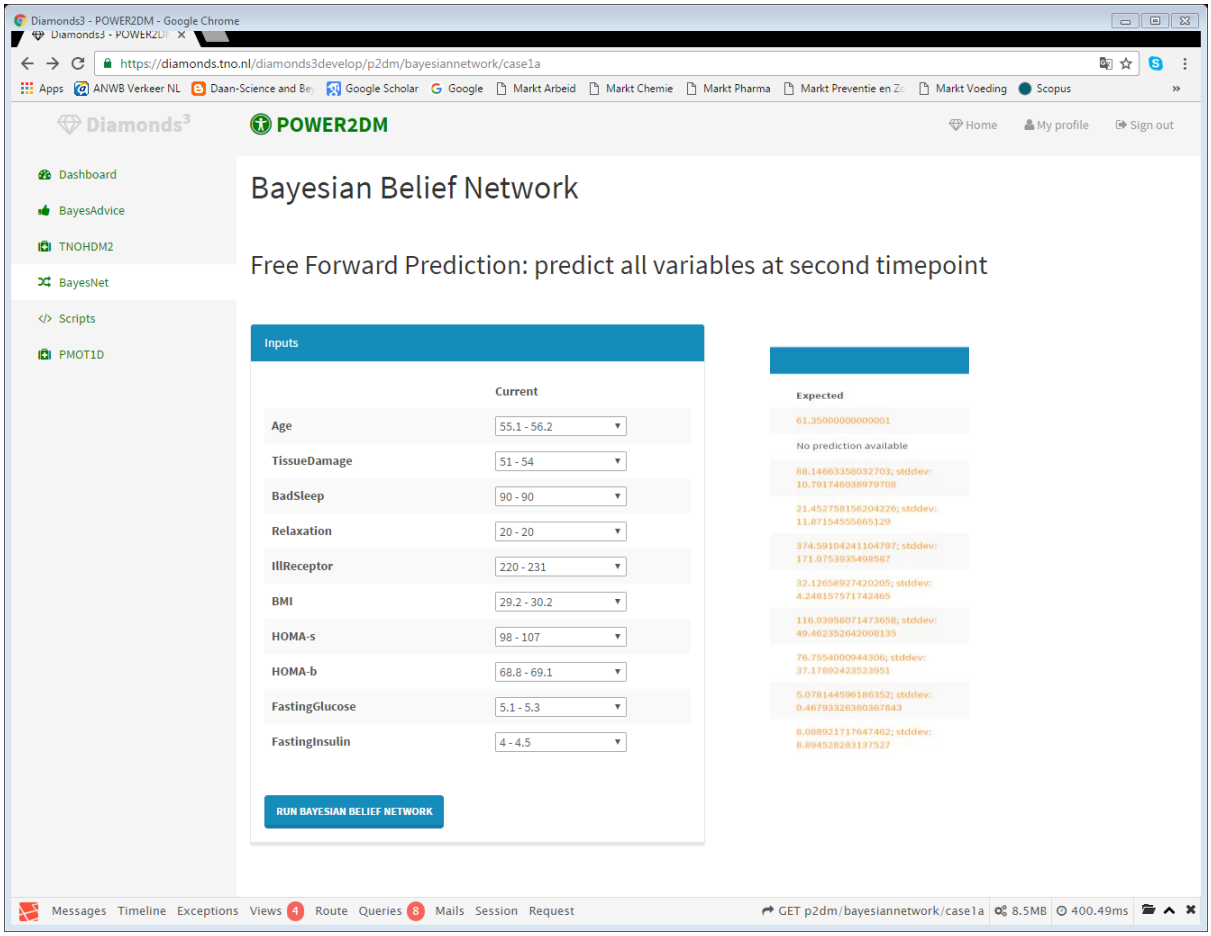


*Figure 3. Illustrative screenshot of MT2D-Marvel predictions. The right panel shows the predictions for the indicated inputs once the button "Run Bayesian Belief Network" is pressed.*

Prediction of outcome expectancies corresponding to POWER2DM use case UC4.3 - Analyze outcome expectancies with MT2D-Marvel, in case goals are reached, in principle is possible using the same dynamic Bayesian network , following the inverse route, i.e.:

- calculate the predicted values according to UC 4.1 explained above (i.e. consequences of continuation of current lifestyle);
- now replace all input values by their respective predicted values (this in fact simulates the predicted situation as current situation)
- then run a new prediction from that situation while enforcing the target value for plasma fasting glucose (i.e. improved health outcome) in the S5 network (i.e. at the end of the prediction period)
- the software will show the associated values of BMI, chronic stress and sleep quality at S5 that correspond to the target glucose value. These can be compared with the input values to obtain targets for lifestyle changes that are necessary to reach the desired improved health outcome.

However, this procedure did not yield satisfactory results principally due to limited data availability in Whitehall II from cases that actually matched this situation of improved health outcomes. Therefore, a different approach was taken as outlined below:

1) A series of outcome values beginning from 4.0 until 10.0 with an increment of 0.1 were iteratively enforced on the output variable plasma glucose and the corresponding values for the lifestyle variables (BMI, chronic stress, and sleep quality) from the S5 network were collected.

2) piecewise linear interpolations were performed to describe these relations (i.e., BMI, stress and sleep quality were expressed as piecewise linear functions of outcome plasma glucose value) (see figure 4 for an example);
3) a lookup table for all outcome glucose values from 4.0 until 10.0 with an increment of 0.1 and the respective values for lifestyle variables calculated from the piecewise linear function was created.

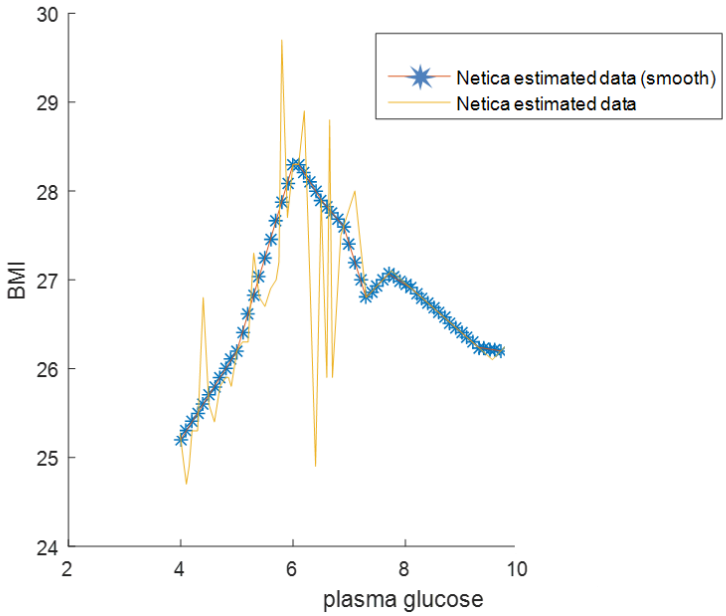


*Figure 4. Example of piecewise linear interpolation to describe estimated (predicted) BMI as a function of outcome plasma glucose, to be used for generating lifestyle advice.*

4) a protocol for prediction of outcome expectancies associated with a desired target value for plasma glucose was established as follows:

- From the lookup table obtain the BMI, chronic stress and sleep quality values for the target glucose value.
- calculate the difference (i.e. the difference between the predicted lifestyle variable values and lifestyle variable values from the lookup table for the target glucose value) as the required change in BMI, chronic stress and sleep quality to be used as a goal for lifestyle modification
- for prediction time windows $T_p$ shorter than the 5.7 years associated with the Whitehall II data, multiply the required changes by a linear proportionality factor equal to $T_p/5.7$.

This procedure was implemented for use in POWER2DM. A target glucose value and prediction time window $T_p$ can be fed into the model and the model will return the required changes in BMI, stress and sleep quality) that are necessary to attain that target glucose value at time $T_p$. The required change in BMI is translated into a required modification of calorie intake and physical activity level that is estimated from the Mifflin-St Jeor model.
Figure 5 shows a screenshot of the current implementation of the MT2D-Marvel outcome expectancy prediction service on the Diamonds3 webserver at TNO (https://diamonds.tno.nl/diamonds3develop/).

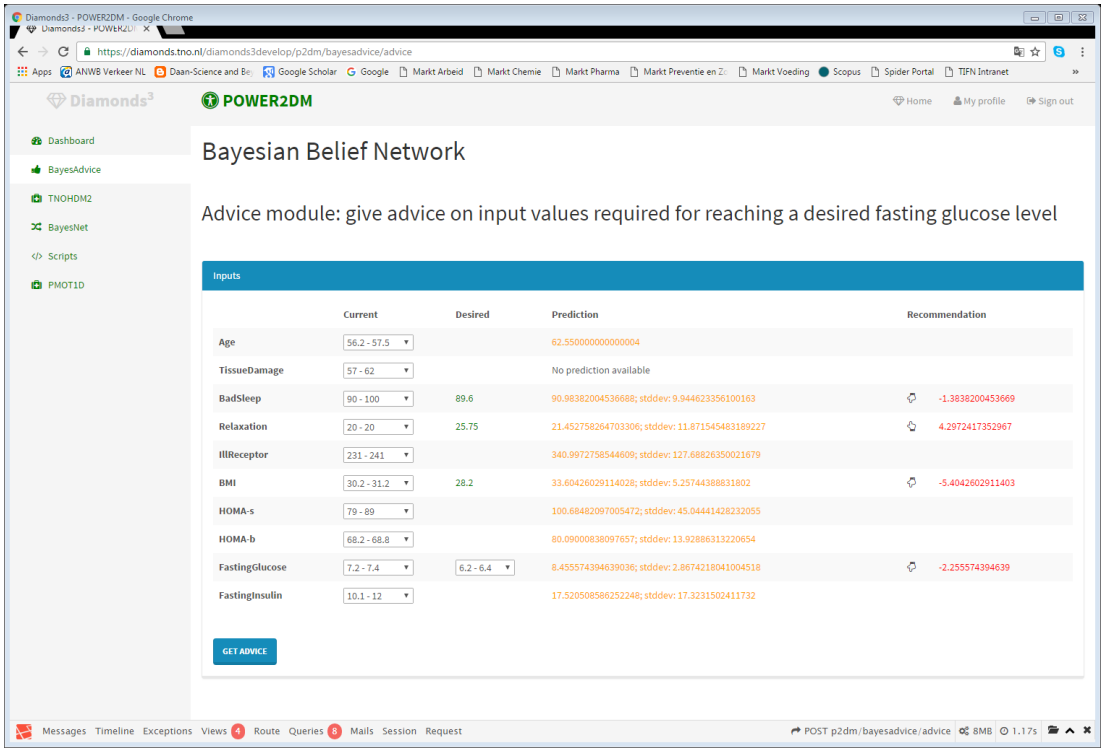


*Figure 5. Illustrative screenshot of the MT2D-Marvel outcome expectancy prediction ("Bayesian Advice module") as implementated on the TNO Diamonds3 server.*

### 2.2.5 Preparation for MT2D-model adaptations for diabetes patients

The original MT2D-Marvel causal loop network was developed for applications with prediabetic subjects. Consequently, the progression of model calibration as documented above was mainly for non-diabetic patients. However, POWER2DM will not include prediabetic subjects but instead will focus on type-1 and type2 diabetic patients. For these patients, we anticipate that two features are important to include in the prediction: 1) the necessity to start medication use; 2) the prediction of lifestyle changes needed to create a situation wherein medication use can be discontinued.

To enable for these predictions, the following steps are currently anticipated:

- Whereas in the Whitehall II data analyses so far, participants using diabetes medication have been excluded, in the upcoming development phase we will expressly include such subjects in the analysis.
- The dynamic Bayesian network will be extended to include a variable "Diabetes Medication use" that has a minimum of 3 states (i.e.: no medication use/oral antidiabetics use/insulin use), and that connects to different variables in both directions, e.g. physiological measures influencing "Diabetes Medication use" and the other way round. Conditional probabilities describing this network are to be derived from the Whitehall II data.

Since in the Whitehall II dataset only approximately 130 subjects (out of more than 9000) documented at phase S5 that they were using diabetes medication, it is anticipated that only a coarse prediction will be feasible. However, this will be compensated by the KADIS short-term prediction model's ability to generate more refined predictions of medication effects.

# 3 LONG TERM PREDICTION MODELS

## 3.1 Introduction

In healthcare practice, long-term prediction models are routinely used to predict the percentage risk of disease or complications depending on current clinical markers and/or lifestyle factors (e.g. smoking) on a longer time horizon, typically 5-10 years. A selection of these models that are relevant to diabetes patients, especially inasfar as they can be used to support self-management e.g. by adding motivation for lifestyle changes, are to be included in POWER2DM.

## 3.2 Available models and model selection

Various risk prediction models for diabetes patients exist. A recent overview is given in (Cichosz, Johansen and Hejlesen 2015). In 2015, more than 250 publications were indexed in Pubmed with keywords "predictive AND model AND diabetes" . These include models for screening on diabetes such as FINDRISC (not relevant for POWER2DM since the project deals with diabetes patients and not with prediabetic persons) and for prediction of long term complications. The latter include models for prediction of retinopathy, prediction of neuropathy (foot ulcers), prediction of nephropathy , prediction of cardiovascular disease, prediction of insulin-associated weight gain, prediction of major outcomes in type-1 diabetes.

### 3.2.1 Retinopathy

Several studies (e.g. (Aspinall et al. 1983, Stratton et al. 2013)) have focused on individualizing the screening interval based on risk factors for retinopathy progression. Hidden Markov models were used (Looker et al. 2013 ) to calculate the probabilities of extending the interval for people with no visible retinopathy. The results showed that extending the interval involved only a small risk. A multiple logistic regression model was constructed (Mehlsen et al. 2012) to adjust the screening interval in low-risk patients. The model on average prolonged the screening interval 2.9 times for type 1 diabetes patients and 1.2 times for type 2 diabetes patients. Predictors included in the model were HbA1c, number of retinal hemorrhages and exudates, longer diabetes duration and blood pressure. These models were judged to be not suited for self management and therefore were not included in POWER2DM.

### 3.2.2 Neuropathy

A study in 2006 (Boyko et al. 2006) followed 1285 diabetic veterans and published a prediction model based on 7 commonly available clinical variables for development of foot ulcers. Later this model was validated and updated in different settings (Monteiro-Soares and Dinis-Ribeiro 2010). Monteiro-Soares and Dinis-Ribeiro included information about patients' footwear and increased the prediction capabilities from an ROC area under the curve (AUC) of 0.83 to 0.88. Yet, no fixed system has eventually been adopted, and the implementation of validation models in clinical practice remains limited. Therefore, these models were not included in POWER2DM.

### 3.2.3 Nephropathy

Several models were developed to predict the progression of kidney disease in people with diabetes (Vergouwe et al. 2010, Keane et al. 2006, Jardine et al. 2012)

The factors most commonly used in these models are gender, age, BMI, diabetes status, blood pressure, serum creatinine, protein in the urine, and serum albumin/total protein. Often the Cox model is used to construct the predictor model—but decision tree and logistic regression have also been used for modeling. C-statistics for these models are generally high and range from 0.56 to 0.94.

The ADVANCE kidney risk prediction model is conveniently available as online tool via the ADVANCE website http://www.advance-trial.com and was judged to be suitable for inclusion in POWER2DM.

### 3.2.4 Cardiovascular Disease

More than a dozen different scores have been developed specifically to predict heart disease in patients with diabetes. The most frequently included predictors are sex, age, systolic blood pressure, cholesterol, and smoking. The most used are those of UKPDS and ADVANCE (UKPDS Group 1991, Stevens et al. 2001, Clarke et al. 2004, Coleman et al. 2005, Guzder et al. 2005, Kengne et al 2011, Hayes et al. 2013). For both scores, convenient online tools exist. Therefore, the UKPDS and ADVANCE cardiovascular risk scores were included in POWER2DM.

### 3.2.5 Insulin-Associated Weight Gain

Data on factors associated with insulin-associated weight gain in 2179 patients with type 2 diabetes were reported in (Balkau et al. 2014). These authors also proposed a model that could explain part of the weight gain. Factors included in this model were HbA1c, BMI at baseline, and information about insulin regimen/dose. Since however their model was not operational for prospective usage in the clinic, it was not included in POWER2DM.

### 3.2.6 Major outcomes in type-1 diabetes

A risk score model for prediction of major outcomes was published in (Sudamah-Muthu et al 2014) . Major outcomes include major CHD, stroke, end-stage renal failure, amputations, blindness and all-cause death. This model is of special interest for POWER2DM because it was specifically developed for type-1 diabetes patients whereas most of the previously discussed risk models were developed either for type-2 or non-specified type of diabetes. Therefore this model was included in POWER2DM.

### 3.2.7 Summary

Summarizing, the following long-term risk prediction models were included for use in the POWER2DM Prediction Services:
ADVANCE cardiovascular Risk engine, ADVANCE Kidney Risk engine, UKPDS cardiovascular risk engine, Major Outcomes T1D model.
The following sections will give information on the background of these selected models and specify the input- and output variables.
In the POWER2DM SMSS, the risk prediction model outputs will be cited to the primary copyrighters (i.e., ADVANCE, UKPDS, Major Outcomes T1D) (This comment is not further repeated in the following sections).

## 3.3 ADVANCE cardiovascular and kidney risk engines

### 3.3.1 Background

The most common cause of ill health in individuals with type 2 diabetes is vascular disease. Reliable tools are needed to help physicians advise their patients about their level of risk of serious vascular events and on the lifestyle and therapeutic measures needed to reduce this risk.
The ADVANCE risk engine is a risk calculator specifically designed around people with type 2 diabetes. It was developed using data for the ADVANCE trial participants without any history of cardiovascular disease at study enrollment. The ADVANCE risk equations are based on risk factors commonly assessed in routine clinical practice.
Literature on the ADVANCE trial can be found on http://www.advance-trial.com/publications/

### 3.3.2 Implementation in POWER2DM

The ADVANCE risk engine is available as a web application proviing the risk of developing cardiac and kidney complications associated with diabetes. The cardiovascular ADVANCE risk engine (http://www.advanceriskengine.com/#page1_cv) provides the risk of having a cardiovascular event over 4 years while the ADVANCE kidney risk engine (http://www.advanceriskengine.com/#page1_kd) provides an estimate of the risk of developing major kidney events in the short term over the next 5 years, or in the longer term (starting with albuminuria). Figures 6 and 7 show screenshots of the Cardiovascular and kidney risk models, respectively. We have contacted the George Institute for Global Health to inquire about possible licensing agreements and API solutions. Full details of the equations have been published, so in principle we can use these to implement the model for the purpose of POWER2DM should the George Institute be unable to answer our needs.

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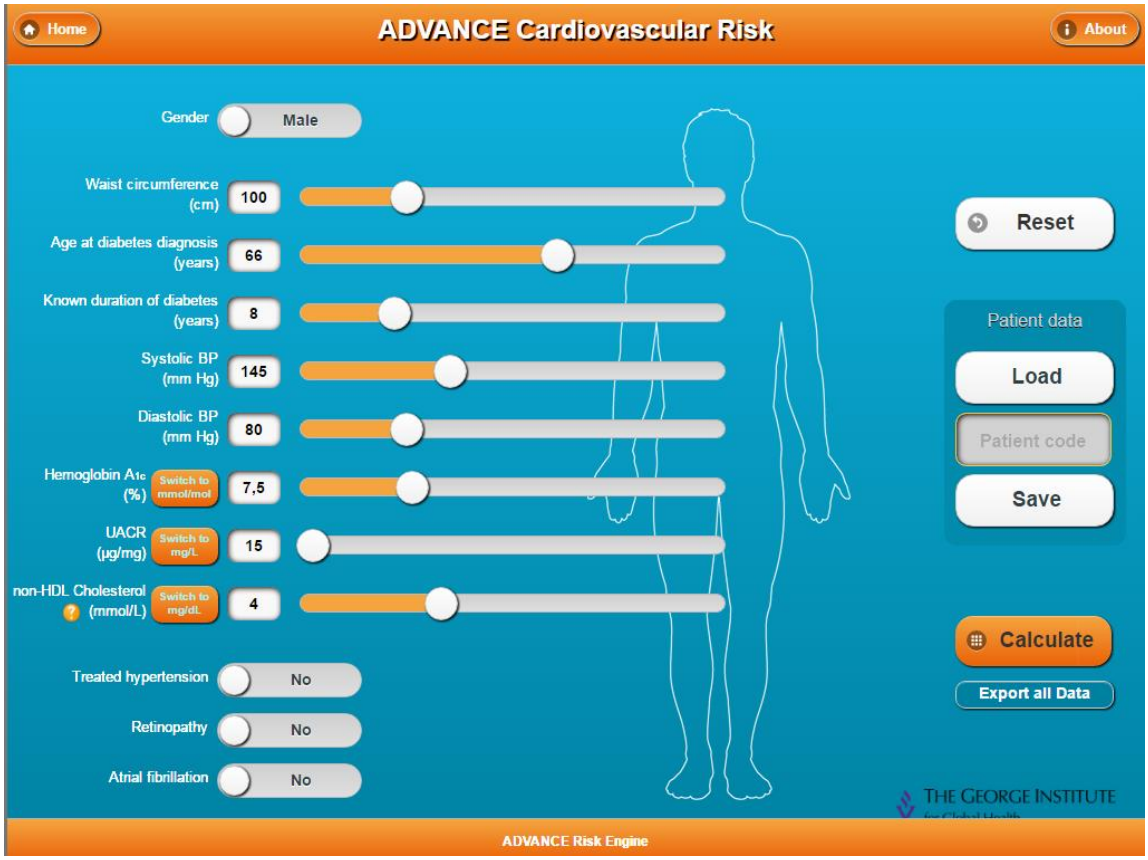



*Figure 6. Screenshot of the ADVANCE Cardiovascular risk engine (web service)*

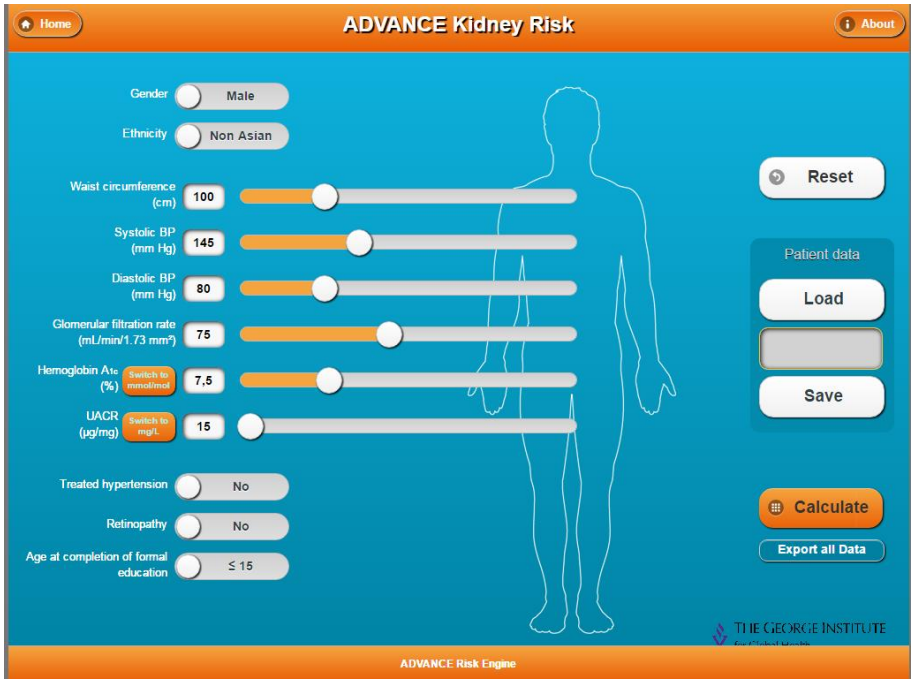



*Figure 7. Screenshot of the ADVANCE Kidney risk engine (web service)*

### 3.3.3 Model Inputs and Outputs

Input and output of the cardiovascular and kidney risk models are defined in Table 3 and Table 4, resp. For both models, if a variable value is beyond the lowest or highest boundary of the indicated range, the risk will be calculated as if the lowest or highest boundary were entered, respectively, and a warning message will be issued.

**Table 3. Inputs (prognostic factors) and outputs (risk of CVD outcomes) of the ADVANCE cardiovascular Risk Engine model, along with valid ranges.**

| ADVANCE CVD risk | Unit | Valid range | Comment |
|---|---|---|---|
| **Input: prognostic factors** | | | |
| Gender | | M/F | |
| Waist circumference | cm | 50-250 | |
| Age at diabetes diagnosis | year | 29-90 | |
| Known duration of diabetes | year | 0-36 | |
| Systolic BP | mmHg | 60-300 | |
| Diastolic BP | mmHg | 40-200 | |
| Glycated haemoglobin (HbA1c) | % | 4-20 | |
| UACR | mg/g | 0.1-500 | |
| non-HDL cholesterol | mmol/L | 0-12 | |
| Treated hypertension | | Y/N | |
| Retinopathy | | Y/N | |
| Atrial fibrillation | | Y/N | |
| **Output:** | | | |
| Predicted 4-year risk of major cardiovascular disease | % | | defined as fatal or non-fatal myocardial infarction or stroke or cardiovascular death |

**Table 4. Inputs (prognostic factors) and outputs (risk of kidney disease) of the ADVANCE Kidney Risk Engine model, along with valid ranges.**

| ADVANCE Kidney risk | Unit | Valid range | Comment |
|---|---|---|---|
| **Input: prognostic factors** | | | |
| **Gender** | | M/F | |
| **Ethnicity** | | Asian/Non-Asian | |
| **Waist circumference** | cm | 50-250 | |
| **Systolic BP** | mmHg | 60-300 | |
| **Diastolic BP** | mmHg | 40-200 | |
| **Glomerular filtration rate** | (mL/min/1.73 mm$^2$ | 15-150 | Calculated from serum creatinine concentration (range ~5-50mg/L) |
| **Glycated haemoglobin (HbA1c)** | % | 3-20 | |
| **UACR** | mg/g | 0.1-500 | |
| **Treated hypertension** | | Y/N | |
| **Retinopathy** | | Y/N | |
| **Age at completion of formal education** | | <=15 / >=16 | |
| **Output:** | | | |
| **Predicted 5-year risk of New-onset albuminuria (UACR >=30 mg/g)** | % | | defined as UACR >=30 mg/g |
| **Predicted 5-year risk of major kidney-related events** | % | | defined as doubling of serum creatinine to ≥ 2.26mg/dL, renal replacement therapy, or renal death |

## 3.4 UKPDS cardiovascular risk engine

### 3.4.1 Background

Risk calculators based on equations from the Framingham Heart Study tend to underestimate risks for people with diabetes as this study included relatively few diabetic subjects. The UKPDS Risk Engine is a type 2 diabetes specific risk calculator based on data from the UK Prospective Diabetes Study that has 53,000 patient years of follow-up.

The UKPDS Risk Engine provides risk estimates and 95% confidence intervals, in individuals with type 2 diabetes not known to have heart disease, for:

- non-fatal and fatal coronary heart disease
- fatal coronary heart disease
- non-fatal and fatal stroke
- fatal stroke

These can be calculated for any given duration of type 2 diabetes based on current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol. Full details of the equations used have been published.

### 3.4.2 Implementation in POWER2DM

The UKPDS Risk Engine v2.0 software was downloaded from the website https://www.dtu.ox.ac.uk/riskengine/ of theDiabetes Trials Unit from the Oxford Centre for Diabetes, Endocrinology and Metabolism. This is standalone software. Figure 8 shows a screenshot of the UKPDS risk calculator. According to the website, the Diabetes Trials Unit offers an API which should allow to integrate the UKPDS risk engine in the POWER2DM Prediction Services. Contacts were established to get an academic license for the UKPDS risk engine but follow-up is limited so far. As a last resource, we might retrieve the full model equations from relevant publications and implement them ourselves.

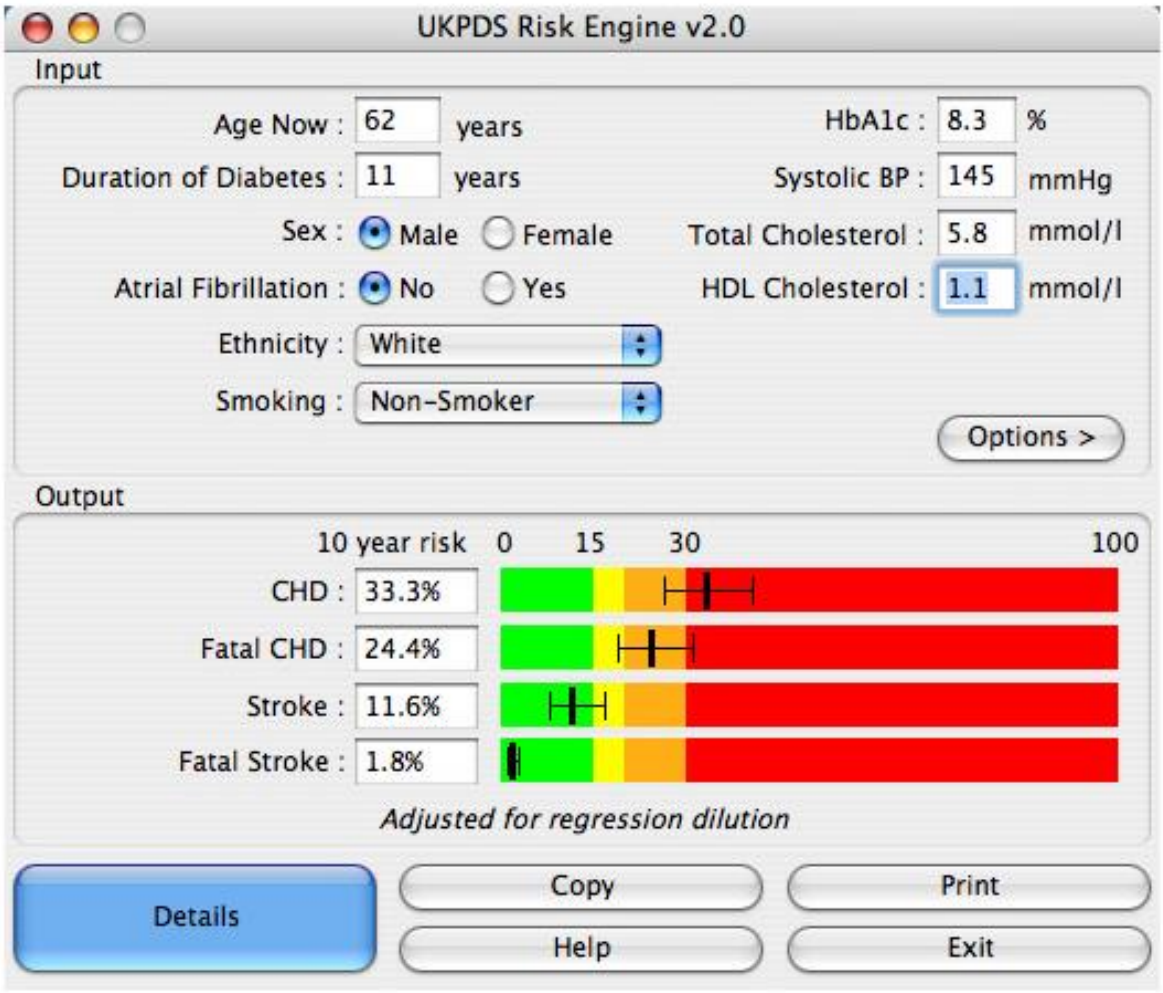



*Figure 8. Screenshot of the UKPDS Risk Engine v2.0*

### 3.4.3 Model Inputs and Outputs

Input and output of the model are defined in Table 5. If a variable value is beyond the lowest or highest boundary of the indicated range, the risk will be calculated as if the lowest or highest boundary were entered, respectively, and a warning message will be issued.

**Table 5. Inputs (prognostic factors) and outputs (risk of CVD outcomes) of the UKPDS Risk Engine v2.0 model, along with valid ranges.**

| UKPDS CVD risk | Unit | Valid range | Comment |
|---|---|---|---|
| **Input: prognostic factors** | | | |
| **Age** | years | 20-120 | Use of the Risk Engine is not recommended for individuals who were under 20 when diabetes was first diagnosed |
| **Glycated haemoglobin (HbA1c)** | % | 2-20 | |
| **Duration of diabetes** | years | >0 | |
| **Systolic BP** | mmHg | 60-250 | |
| **Sex** | | M/F | |
| **Atrial fibrillation** | | Y/N | |
| **Total cholesterol (TC)** | mmol/l | 1-15 | |
| **HDL-cholesterol** | mmol/l | less than TC | |
| **Ethnicity** | | White/Afro-Caribbean/Asian-Indian | |
| **Smoker** | | Non-smoker/Ex-smoker/Current smoker | |
| **Risk interval** | years | >=1 | |
| **Output:** | | | |
| **predicted risk of CHD** | % | | also calculates approximate 95% confidence interval for the estimated risk |
| **predicted risk of fatal CHD** | % | | also calculates approximate 95% confidence interval for the estimated risk |
| **predicted risk of stroke** | % | | also calculates approximate 95% confidence interval for the estimated risk |
| **predicted risk of fatal stroke** | % | | also calculates approximate 95% confidence interval for the estimated risk |

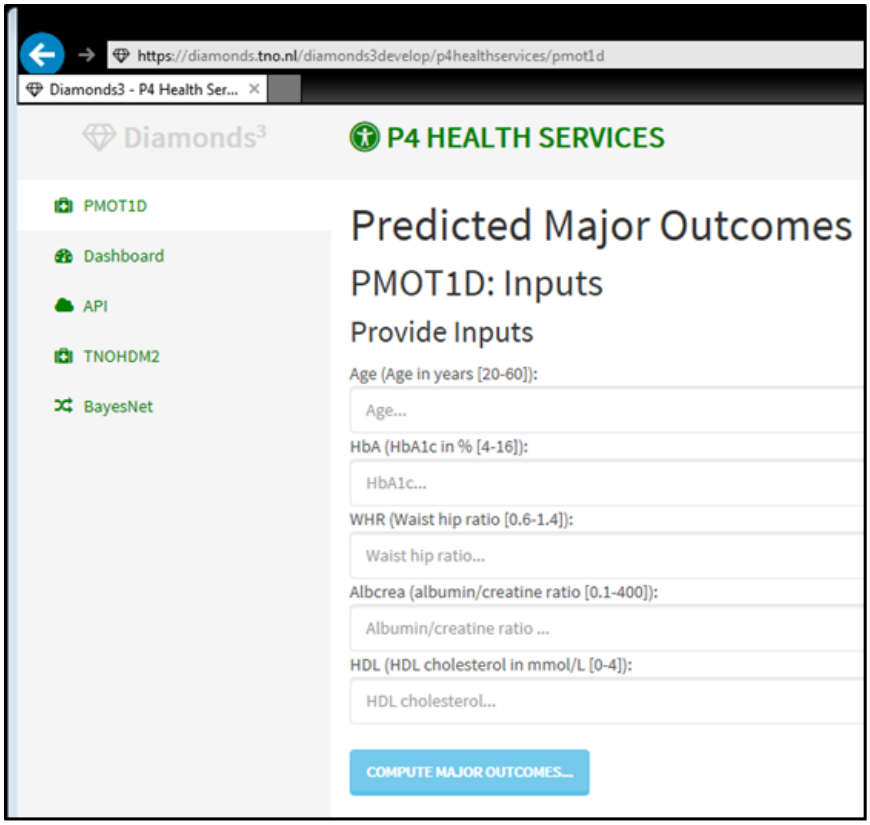
## 3.5 Major Outcomes T1D model

### 3.5.1 Background

Type 1 diabetes is associated with a higher risk of major vascular complications and death. A reliable method that predicted these outcomes early in the disease process would help in risk classification. Sudamah-Muthu et al. therefore developed such a prognostic model based on data from from 1,973 participants with type 1 diabetes followed for 7 years in the EURODIAB Prospective Complications Study, and quantified its performance in 3 independent prospective cohorts: the Pittsburgh Epidemiology of Diabetes Complications study (EDC, n=554), the Finnish Diabetic Nephropathy study (FinnDiane, n=2,999) and the Coronary Artery Calcification in Type 1 Diabetes study (CACTI, n=580) . Prognostic factors were age, HbA1c, WHR, albumin/creatinine ratio and HDL-cholesterol level. The discriminative ability of the model was adequate, with a concordance statistic (C-statistic) of 0.74. Discrimination was similar or even better in the independent cohorts, the C-statistics being: EDC, 0.79; FinnDiane, 0.82; and CACTI, 0.73.

### 3.5.2 Implementation in POWER2DM

The full model equations were obtained from the first author upon request. The Major Outcomes T1D prediction service was programmed and implemented on a server at TNO, where it can be launched by the POWER2DM system via an API.
Figure 9 shows a screenshot of the development version of the Major Outcomes T1D prediction service available on the Diamonds webserver at TNO https://diamonds.tno.nl/diamonds3develop/



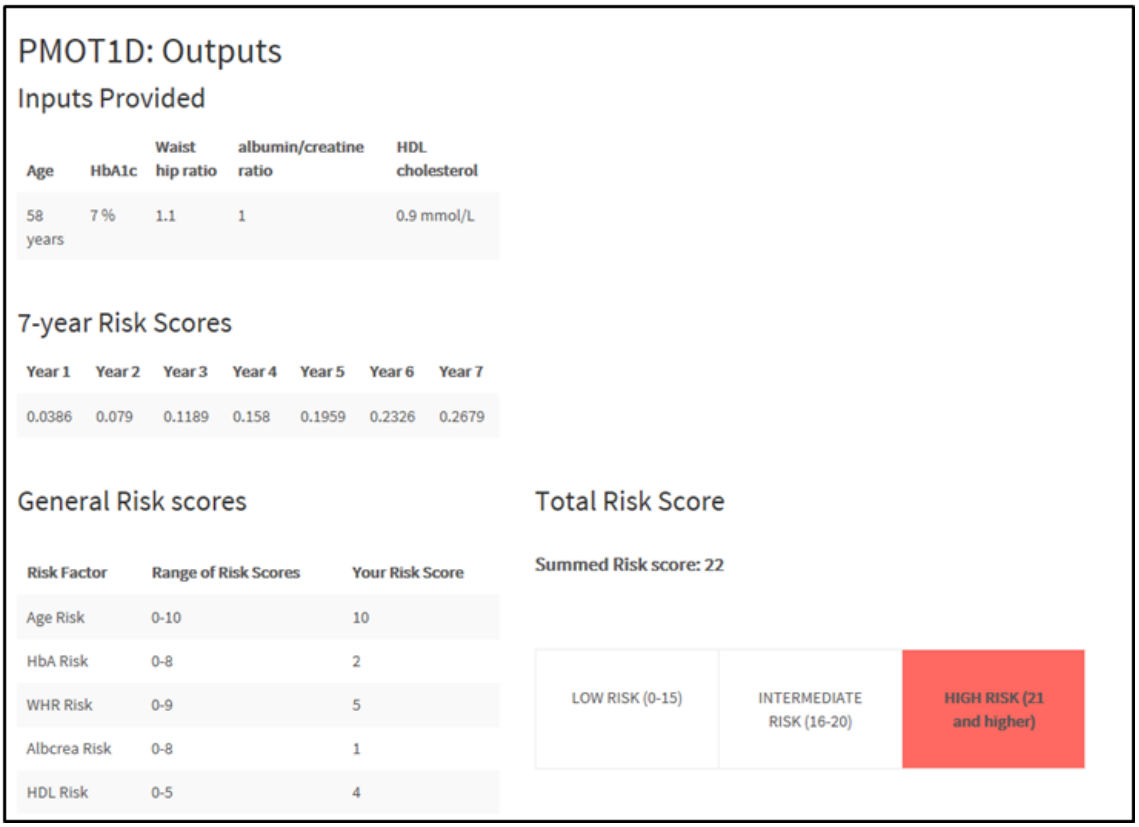




*Figure 9. Screenshot of the Major Outcomes T1D prediction service web interface. Top panel: input screen. Bottom panel: output screen*

### 3.5.3 Model Inputs and Outputs

Input and output of the model are defined in Table 6. If a variable value is beyond the lowest or highest boundary of the indicated range, the risk will be calculated as if the lowest or highest boundary were entered, respectively, and a warning message will be issued.

**Table 6. Inputs (prognostic factors) and outputs (risk of major outcome) of the Major Outcomes T1D model, along with valid ranges.**

| Major Outcomes T1D | Unit | Valid range | Comment |
|---|---|---|---|
| **Input: prognostic factors** | | | |
| **Age** | years | 20-60 | |
| **Glycated haemoglobin (HbA1c)** | % | 4-16 | |
| **Waist-hip ratio** | value | 0.6-1.4 | |
| **Albumin/creatinine ratio** | mg/mmol | 0.1-400 | |
| **HDL-cholesterol** | mmol/l | 0-4 | |
| **Risk interval** | years | 3-7 | |
| **Output:** | | | |
| **predicted risk of major outcome at risk interval** | % | | Major outcomes include major CHD, stroke, end-stage renal failure, amputations, blindness and all-cause death |

# 4 Further work/open issues:

The MT2D-Marvel model predictions will be validated on the Whitehall II cohort data via n-fold cross validation procedures.

# 5 Literature

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