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A knowledge-based decision support system to support family doctors in personalizing type-2 diabetes mellitus medical nutrition therapy

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ABSTRACT

Background: Type-2 Diabetes Mellitus (T2D) is a growing concern worldwide, and family doctors are called to help diabetic patients manage this chronic disease, also with Medical Nutrition Therapy (MNT). However, MNT for Diabetes is usually standardized, while it would be much more effective if tailored to the patient. There is a gap in patient-tailored MNT which, if addressed, could support family doctors in delivering effective recommendations. In this context, decision support systems (DSSs) are valuable tools for physicians to support MNT for T2D patients – as long as DSSs are transparent to humans in their decision-making process. Indeed, the lack of transparency in data-driven DSS might hinder their adoption in clinical practice, thus leaving family physicians to adopt general nutrition guidelines provided by the national healthcare systems.
Method: This work presents a prototypical ontology-based clinical Decision Support System (OnT2D- DSS) aimed at assisting general practice doctors in managing T2D patients, specifically in creating a tailored dietary plan, leveraging clinical expert knowledge. OnT2D-DSS exploits clinical expert knowledge formalized as a domain ontology to identify a patient's phenotype and potential comorbidities, providing personalized MNT recommendations for macro- and micro-nutrient intake. The system can be accessed via a prototypical interface.
Results: Two preliminary experiments are conducted to assess both the quality and correctness of the inferences provided by the system and the usability and acceptance of the OnT2D-DSS (conducted with nutrition experts and family doctors, respectively).
Conclusions: Overall, the system is deemed accurate by the nutrition experts and valuable by the family doctors, with minor suggestions for future improvements collected during the experiments.

1. Introduction

Type-2 Diabetes Mellitus (T2D) is a non-communicable disease affecting more than 537 million people aged between 20 and 79 years in the world [1]. It is estimated that the number of people affected by T2D will increase significantly to 643 million in 2030, reaching 783 million in 2045. Taking into account that both Asian and Pacific area countries have shown a relevant growth in the number of diabetic patients [2], T2D has reached epidemic proportions, and it considerably impacts countries' healthcare expenditure [1,3]. T2D needs to be treated adequately to avoid chronic complications (e.g., damage to the heart and cardiovascular system, kidney failures, impairments to vision, impairments to the lower limbs) and acute health consequences (such as difficulties related to ketoacidemic and hypoglycaemic statuses and hyperosmolar coma). Diabetes-related conditions account for 1.5 million deaths every year globally [3]. Italy counts more than 4 million diabetic patients (6.8 % of the population), with 350,000 new diagnoses every year [4]. The recent COVID-19 pandemic aggravated the mortality rate of diabetic patients in Italy, with 2020 accounting for 97,000 deaths for which diabetes was deemed the main or concurrent cause [4].

Patients affected by T2D can be treated with Medical Nutrition Therapy (MNT), consisting of a nutritionally balanced and clinically

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developed diet, with regular physical activity – in most cases, even before considering a pharmacological and insulin-based therapy [5]. For this reason, many countries have developed national guidelines to support diabetic patients with general dietary recommendations to avoid health complications and support the patient's day-to-day management of the disease. These guidelines considerably differ among them since they address population or country-specific dietary habits and share some commonalities – for example, the definition of the "diabetic condition" and some food categories and nutrients to be included in a daily diet [6]– and over the years, they proved to be an efficient tool to provide patients with basic support towards the day-to-day management of T2D. Local guidelines are also adopted by family physicians or general practice doctors to guide their decisions in managing diabetic patients since not all clinicians are trained to provide patient-tailored MNTs. However, guidelines cannot provide tailored diets. Thus, they are not an effective tool for the operational administration of an MNT – in particular, considering that diabetic patients' glycemic response to diet significantly varies from person to person [7] and considering that patients may also be affected by other comorbidities. Nevertheless, in Italy (as in some European countries), family physicians and general practice doctors have to face a healthcare framework characterized by multimorbidity and play a pivotal role in primary care: as such, these clinicians are committed to answering patients' requests for tailored therapies [8].

Nowadays, digital and AI-based technologies can help clinicians work at different levels, including primary care; furthermore, health digitalization could reduce the costs of chronic patients' treatment and provide a "quick fix" for the generalized medical shortages. In particular, from a Healthcare 5.0 perspective, AI-enabled medicine can foster the generation of novel patient-based therapies [9]. Moreover, data-driven AI applications are adopted in many diagnostic tasks [10] and imaging [11] with considerable satisfaction. However, some authors underline a reluctance to change in healthcare (for instance, in adopting innovative digital solutions in clinical practice) [12]; in particular, this phenomenon is also true for the Italian context [13]. Among the reasons that prevent the wide adoption of AI-based solutions in this field is the lack of transparency in the decision-making process (named "black box" model by Goodman and Flaxman), which plays an essential role [14]. A possible solution to this problem consists of adopting explainable AI (xAI) tools, for which the possibility to provide human-understandable explanations of the inferences generated by a machine could prove essential for adopting digital technologies in healthcare [15]. In such contexts, domain ontologies can be adopted as part of AI systems due to the possibility of inferring new information via monotonic reasoning [16] to develop them. Also, the transparent reasoning based on inference (somehow resembling human inference capabilities [17]) and ontology engineering (which heavily relies on the formalization of experts' knowledge) make domain ontologies suitable to foster the adoption of xAI-based systems in healthcare.

Similar considerations can be drawn for MNT devoted to supporting T2D patients – there exists a lack of fully reliable and expert knowledge-based tools to support family doctors in managing tailored MNT for T2D patients. Thus, this work introduces a prototypical ontology-based clinical Decision Support System (DSS) – named OnT2D – to support family physicians and general practice doctors in providing diabetic patients with personalized dietary guidelines, considering the patient's condition and comorbidities. To the best of the authors' knowledge, no knowledge-based tool can currently support family doctors in providing tailored MNT recommendations at the macro- and micro-nutrient level for patients affected by T2D. The adoption of knowledge-based technologies is motivated by the lack of datasets that collect MNT data for T2D patients specifically related to MNT. Among the datasets addressing T2D [18,19], consider MNT or the clinical parameters adopted in this work since they are mostly devoted to predicting the disease. Indeed, as also pointed out in Refs. [20,21], the absence of datasets for the training of data-driven algorithms is a major concern – especially for the case of T2D patients [20], but also impacting Type 1 Diabetes [22] – due to ethical or data privacy restrictions as well as to the lack of highly accurate, complete and unbiased data [21]. In fact, a further complication in the data collection for MNT recommendations lies in the importance of considering population-based aspects alongside the specific type of diabetes since also cultural aspects and ethnicity play a major role in nutrition [20,21,23,24].

Therefore, the DSS leverages ontological representations of the relevant domain knowledge and a rule engine developed with clinical domain experts. In this way, the limitations related to the current state of the datasets can be overcome, and the clinicians' need for an accountable and explainable DSS can be satisfied through a knowledge-based system exploiting semantic reasoning to generate interpretable and explainable MNT inferences.

The main contribution of this work is the ontological framework (formalizing clinicians' expert knowledge) on MNT for T2D patients and its adoption in a prototypical DSS. Two validations have been conducted with clinical personnel with the aim of a) assessing the correctness of the knowledge-based system's inferences with MNT experts and b) investigating usability and job relevance feedback with a sample of end users (family doctors). The ontological layer is developed relying on a collaborative and agile ontology engineering methodology (OEM), which fosters the involvement of clinical personnel from the early stages of the engineering process. The remainder of this article is organized as follows: Section 2 surveys some of the most relevant DSSs to support T2D management, illustrating the methodological differences between them and OnT2D's development. Section 3 describes the collaborative ontology engineering of OnT2D, specifying the clinical concepts adopted, underlining the role of clinical experts in light of the AgiSCOnt OEM [25], and verifying the inferences generated by the resulting ontology; the prototypical application of OnT2D-DSS is also presented. Section 4 proposes a preliminary validation of OnT2D's efficacy from an MNT perspective by presenting an experiment aimed at evaluating the correctness and effectiveness of the DSS's recommendations with 11 MNT experts (dieticians and clinical nutritionists operating in hospitals and with experience with T2D patients) and its results; in this section, a preliminary validation of the OnT2D-DSS application is also performed with 5 family doctors. Leveraging the results, some considerations on OnT2D are discussed in Section 5, and the Conclusions summarize the main outcomes of this work and draft the next developments.

2. Related work

In this Section, a few AI-based approaches for managing T2D, supporting diabetic patients, and helping clinical personnel in various disease-related tasks are presented. The examples are discussed in light of recent literature reviews on the adoption of AI to T2D.

2.1. AI for diabetes: examples of knowledge- and data-driven DSSs for diabetic patients

As highlighted in the Introduction, AI can support the development of DSS aimed at managing different aspects of T2D chronic disease. As pointed out by Donsa and colleagues [26] in 2015, decision support applications for diabetes are used for *patient self-management* (which includes medication support and therapy control, optimization of insulin therapy, management of the disease on a long term in outpatient care, and at home) and for *institutional care* (encompassing systems devoted to supporting the clinical settings' workflow and clinical evidence-based DSSs). Also, according to the 2017 review by Contreras and Vehi [27], the total number of scientific works addressing the study, development, and use of AI for decision support for diabetes management surpassed 10,000. The review underlines that the most investigated topics are blood glucose control and prediction, prompt detection of adverse glycemic events, insulin calculators, meal diaries and specific nutrient intake predictors (caloric intake, mostly), physical exercise, and lifestyle recommender systems. Findings indicate that AI capabilities are adopted in different aspects of disease management – but not MNT. However, several works exist that exploit ontological representations of diabetes and its related domains and tackle – from different perspectives – the problem of T2D patients' nutrition. In Table 1, a few examples of both types (data-driven and knowledge-based systems) are presented and discussed.

2.2. Consideration on the use of AI for diabetes: from diagnosis to nutritional recommendations

As highlighted in Ref. [26], both types of AI-based DSS (i.e., *data-driven* and *knowledge-based* DSSs) are either dedicated to support patients in the daily management of T2D, or they are developed to help clinical personnel in some specific tasks. In line with Contreras and Vehi's findings [27], all the data-driven solutions exploit ML to predict or support the diagnosis T2D (or related comorbidity) – [28–33] – with one work investigating blood glucose control ([34]). In terms of prediction of T2D onset or T2D-related comorbidity, the possibility to leverage a significant amount of data is pivotal (as in, e.g., Refs. [29,32]) and seems to constitute a promising approach in promptly identifying T2D (or comorbidity) in a population using a limited number of common parameters. The increasing availability of high quality health datasets makes it possible to train and refine ML methods to promptly diagnose T2D, thus supporting the national healthcare systems in managing this disease and limiting its long-term effects on the population. This is ultimately the purpose of the majority of the works reported in the upper portion of Table 1 ([28–33]): although the predictive performances are not always excellent, they are projected toward a significant improvement in the accuracy levels, supported by large amounts of organized data (as underlined in Ref. [35]). According to Ref. [27], blood glucose control is one of the most investigated aspects, as represented by the work of Daskalaki and colleagues [34], who leveraged a reinforcement learning algorithm to develop a patient-centered and adaptive blood glucose control strategy.

The vast majority of the solutions portrayed in the data-driven portion of Table 1 are developed to support clinicians in their activities, thus, they fall under the *institutional care* group of AI-based solutions. These solutions can actively support diabetologists and endocrinologists in the prompt identification of T2D onset in many segments of the population; however, among their limitations, most of them require extensive validation involving clinical experts, as well as (in some cases) the fine-tuning of the adopted methods. Also, although some works are recent, some papers are focused on comparing the performances among different types of methods ([28,30–33]): this is essential to enable the development of ML-based clinical solutions, but it also highlights the role of data-driven application in clinical practice. The research for this type of solution is still at an early stage and requires close collaboration with clinical experts to make some steps forward [36]. A notable absence in the first portion of Table 1 is MNT, which – in line with the findings of the most recent reviews consulted [27,35,37] – is less investigated through the means of data-driven methods. As underlined in these three reviews, the task of providing MNT recommendations is not among those typically performed with data-driven techniques, which are adopted in the context in which datasets are available (or data can be collected); on the contrary, in the case of MNT recommendations for T2D patients, there are no suitable datasets available [20,21] – a problem also characterizing another nutritional recommendation- and AI-related research area, precision nutrition [38].

On the contrary, the second portion of Table 1 (knowledge-based DSSs) underlines domain ontologies' role in formalizing MNT knowledge. Nutritional recommendations are generally aligned with (national) clinical standards or guidelines, with some personalization features. A recent review [39] underlined the necessity of balancing general local guidelines with patient-tailored MNT personalization, developing patient-centered systems capable of providing nutritional therapeutic recommendations that take into account the different comorbidities characterizing diabetic patients. A significant difference among the DSSs depicted in this portion of Table 1 is that the granularity of the recommendation can vary from food items (i.e., specific foods) to full diets (with daily meal recommendations). In these works, the formalization of T2D's concepts and food items is fundamental to match the patients, their physiological status, and dietary recommendations. The works share the adoption of patient's clinical data (although the works make use of different data [39]) and leverage expert knowledge gathered from the scientific literature to develop an ontological framework (and rules) to infer suitable food items options for specific patients. Differently from data-driven DSSs, the knowledge-base systems are mostly dedicated to support patients in self-managing the disease and its impacts on daily habits ([40–43]), with one work aimed at developing an upper-level clinical ontology for the Chinese population [44]. The availability of biomedical ontologies since the early 2000s made it possible to represent not only T2D but also to include some comorbidities in the domain ontologies (e.g., Refs. [42–45]). Nonetheless, it is worth observing that developing and maintaining ontologies comes with a cost in terms of human resources since updating both TBox and rule engines requires an effort.

Interestingly, all the works relied on entailment to generate safe inferences – mostly in the form of "if-then" rules or class restrictions. A rule-based recommendation's transparency could explain the prevalence of such systems over more advanced AI techniques. Rules are explicit, results produced by these systems are auditable, and human users can potentially trace the inference mechanism to fully understand the inference produced through the rules. In general, ontologies and rules enable the personalization of services because of their logical structure, which ensures that conclusions drawn from the data are justified [46]. These considerations strengthen the role played by domain experts in ontology-based clinical DSSs [47], underlining the need for expert guidance in the development of xAI tools in clinical contexts.

All the knowledge-based DSSs rely on ontological reasoning to draw inferences to support the management of T2D. However, not all the ontologies were developed with domain experts (a pivotal characteristic of ontology engineering [48]), nor did they undergo validation with end users or evaluation with clinical personnel [39]. Delving into the concepts described in the selected works, the conceptualization of "food items" cannot properly support clinical personnel in the development of suitable and balanced MNT diets: DSSs conceived for patients can hardly be adapted into clinical DSSs. In the case of T2D's MNT, the number and time of meals and the amount of macro and micronutrients per meal and portions need to be adapted to the patient's metabolic targets or oral or insulin therapy [49]. Concerning the identification of BMR – a critical metric to assess a person's caloric intake – it is worth noting that only one work [50] resorts to equations to calculate it. However, as observed by dieticians [51], the sole Harris-Benedict equations are insufficient to predict the correct BMR – in particular for patients characterized by obesity. Moreover, none of the articles tackles the anthropometric phenotypes of patients, which can provide important indications for the composition of a tailored diet [52]. The unspecified concepts and relationships characterizing most of the abovementioned works may also be caused by the lack of a rigorous engineering process – since structured OEMs can foster the elicitation of knowledge and its conceptualization in several fields [53], including healthcare.

It is fundamental to observe that the exemplifying works reported in Table 1 do not cover the totality of AI-based applications related to T2D. Moreover, it is also necessary to observe that data-driven solutions are currently employed in a variety of tasks pertaining to nutrition (e.g., food recognition, dietary assessment of meals, nutrition-related diseases prediction, and personalized nutrition): however, according to some authors [21], in all these research areas the role of clinical experts and national nutritional guidelines remains marginal in the design of data-driven system.

Table 1
Some examples of AI-based DSSs devoted to support T2D patients and clinicians (Abbreviations adopted in the Table: BF: Bootstrap forest; DT: Decision tree; ETC: Extra tree classifiers; LASSO: Least absolute shrinkage and selection operator; LR: Logistic regression; XGB: Extreme gradient boosting; RF: Random forest).

	Purpose	Target users	Addressed comorbidities	Methods and techniques	Validation	Limitations
Data-driven DSSs						
[34]	Insulin (basal rate and bolus dose) adaptation algorithms for glucose control, based on reinforcement learning for diabetic patients.	Patients	–	Two Actor-Critic learning algorithms used for the update of basal and bolus insulin infusion recommendation.	The algorithms are tested with simulated patients (10 adults, 10 adolescents, 10 children), including uncertainties in their meals.	The system performs more than adequately with children, adequately with adults and adolescents. The learning algorithms need to be tuned on patient information to achieve individualized learning rates.
[28]	A ML model to predict hypoglycemia in T2D patients based on blood glucose level.	Patients	–	Binary classification based on patient's self-monitored blood glucose level and the related timestamp. Four ML algorithms were tested and trained – RF, SVM, k-nearest neighbor, naïve Bayes.	The prediction model is tested with 11 self-reported blood glucose levels over 7 days. The results from the SMV are compared with 3 endocrinologists opinion, observing the same data sample. The model shows a higher sensitivity than experts, while experts show a higher specificity.	Random forest and SVM showed better accuracy than the other models. Very limited sample and expert panel for the validation; unclear origin of the sample data (simulated or from real patients?).
[29]	A population-level ML model for the prediction of T2D onset (5 years before the disease onset) using administrative health data.	Clinical personnel or healthcare system	–	Leveraging demographic, laboratory, drugs, healthcare system interactions data from more than 2 mil. non diabetic individuals, a gradient boosting decision tree is trained to predict onset (and costs) of T2D.	The model is validated with data from more than 2 mil. individuals from 2009 to 2016 and it proved effective in its predictive goal.	Potential misclassification for Type 1 diabetic patients; heterogeneity of the administrative input data and lack of important indicators (e.g., BMI).
[30]	A set of ML models for the prediction of end-stage renal disease in newly diagnosed T2D patients.	Clinical personnel or healthcare system	End-stage renal disease	LR, ETC, RF, gradient boosting decision tree, light gradient boosting machine, XGB.	A 10-year study with more than 53.000 T2D patients' longitudinal data from electronic health records was able to show XGB performs better than the other algorithms.	High variability in the availability of electronic health records. External and more extended validation studies required. It lacks a complete validation and clinical experts' opinion.
[31]	A risk prediction model for diabetic retinopathy in T2D Chinese patients.	Clinical personnel or healthcare system	Diabetic retinopathy	XGB, RF, recursive feature elimination, backpropagation neural network, LASSO	Limited to the evaluation of the models (accuracy, precision, F1 score, balanced accuracy). Clinical experts not involved.	Promising in supporting clinicians in identifying diabetic retinopathy; it lacks a complete validation and clinical experts' opinion.
[32]	A neural network-based approach using clinical and personal information to predict or support the diagnosis of T2D.	Clinical personnel or healthcare system	–	It combines generic (gender, age) and physiological data (HDL, blood pressure, BMI, etc.) – more than 48k samples – to predict T2D onset leveraging a neural network.	Limited to training and calibration of the model. Clinical experts not involved.	Although promising, it lacks an extended validation and experts' opinions comparison.
[33]	A DSS leveraging hematological parameters to support T2D diagnosis; the study evaluates different ML techniques.	Clinical personnel or healthcare system	–	9k complete hematological datasets (half T2D patients) processed with LR, DT, and BF.	A comparison of the predictive performance of the three methods was performed. Clinical experts not involved.	Not all hematological parameters were considered (e.g., HbA1c); sample not representative of the cultural variety of the selected population. It lacks a complete validation and clinical experts' opinion.
Knowledge-based DSSs						
[50]	A fuzzy ontology-based food recommender system for the Taiwanese population.	Patients	–	The system combines ontological classifications of food items with fuzzy inference mechanisms to provide a set of food items.	The system is tested by producing dinners for 2 volunteers. Clinical experts not involved.	Focus on meal(s) recommendation and a limited set of macro- and micro-nutrients (carbohydrates, fats, proteins).
[40]	A DSS to support diabetic patients in managing their diet by suggesting recipes and providing carbohydrates count.	Patients	–	Domain ontology combined with rule-based reasoning (not performed within the ontology)	–	Focus on a single nutrient (carbohydrates) and on specific food items recommendations. Significant efforts in the

(*continued on next page*)

Table 1 (*continued*)

	Purpose	Target users	Addressed comorbidities	Methods and techniques	Validation	Limitations
						maintenance of the knowledge base.
[45]	A type-2-FML-based fuzzy ontology-based DSS to assess the level of healthiness in a patient's diet, based on his/her collected meal records.	Not specified	Cardiovascular diseases (not further specified)	Fuzzy rules are used to model the nutrients' percentages and to infer for each food consumed whether it falls in a specific category.	7 healthy students' dietary records (3 meals per day); the DSS's outputs are then compared to those provided by 3 dieticians.	The DSS does not provide nutritional recommendation; rather, it is devoted to assess the quality of a patient's diet. It does not take into account nutritional restrictions caused by particular health conditions.
[41]	An ontology and Case-based reasoning DSS to recommend menus (set of food items) for diabetic patients.	Patients	–	Combines rule-based and case-based reasoning to produce a menu.	The DSS produced a menu for 1 patient and the output is assessed by 4 experts.	Unclear role of the reasoning techniques involved, the content and extent of the knowledge base is not specified.
[42]	A DSS combining ontology and Decision Tree to infer personalized nutritional recommendations (recipes) for persons with chronic conditions (among which, diabetic patients) in Taiwan.	Patients	Hypertension, hypercholesterolemia.	Ontology engineering based on local clinical guidelines, combined with 7-days user's dietary records.	Accuracy of the prediction evaluated with 10 patients. Clinical experts not involved.	Limited number of comorbidities. The role of Decision tree is confined to the classification of patients on the basis of their physiological condition and 7-days dietary records.
[43]	An ontology-based DSS relying on clinical expert knowledge to support the personalization diet (set of recipes) of patients with chronic conditions.	Patients	Osteoporosis, IBS syndrome, gastritis.	Ontology engineering based on clinical evidences, scientific literature, and domain experts.	–	Significant efforts in the maintenance of the knowledge base (including rules).
[44]	An ontology-based DSS for the Chinese population, capable of predicting T2D and support treatment (including local remedies).	Clinical personnel or healthcare system	Retinopathy, some hormonal dysfunctions, and T2D-related conditions (e.g., polydipsia, polyuria, etc.).	Ontology engineering based on clinical evidences, local clinical guidelines, scientific literature, and domain experts.	–	Mostly focused on terminology, it lacks an adequate number of rules for practical use.

2.3. Contributions of OnT2D

Considering the observations conducted in the previous subsections, the hesitancy in adopting AI-based solutions characterized by a "black box" in some clinical contexts (including nutrition care [24]), the availability of clinical guidelines for T2D MNT (and, on the contrary, the lack of MNT datasets specific for the Italian population), the proposed DSS relies on a domain ontology. The proposed ontology (OnT2D) differs from the works presented in the second portion of Table 1 since it is developed with domain experts (diabetologists and clinical personnel operating with diabetic patients) and with the end-users (family doctors) in mind. Therefore, the OnT2D-DSS application exploiting the ontology aims to identify the correct intakes for micro- and macro-nutrients, thus adopting a nutrient-centered perspective. In terms of Donsa and colleagues' classification [26], OnT2D is developed to support family doctors (who do not necessarily have notions of MNT) to manage T2D patients by providing tailored recommendations, taking into account their health conditions as a whole – thus, also considering comorbidities [54]. This approach enables family doctors to play a pivotal role in composing patients' diets and assuring their adherence to dietary guidelines [55]. Therefore, the proposed DSS involves domain experts in *all phases* of ontology engineering and relies on two sets of clinical experts to validate the knowledge base and the inferences generated by the DSS and to assess the application's acceptance (usability and relevance) while adopting classical entailment to a transparent assessment of the system and its rules.

3. Development of OnT2D

The ontology engineering process for OnT2D took advantage of an agile and collaborative OEM – AgiSCOnt [25]. This methodology relies on domain experts to elicit and conceptualize experts' domain knowledge into a conceptual map (Step 1 – domain analysis and conceptualization). The conceptual map is later developed into an ontology, tested to investigate its compliance with Competency Questions (CQs), and evaluated against a set of use cases (Step 2 – Development and test). Finally, the ontology prototype is further analyzed by domain experts to check for missing concepts and possible updates, then it is adopted as the backbone of a DSS and used – in this specific case, OnT2D is used to configure the diet of selected patients leveraging the OnT2-DSS (Step 3 – Ontology use and updating). Fig. 1 represents AgiSCOnt's steps applied to the development of OnT2D.

The methodology leverages an iterative and collaborative approach to refine the conceptual map until all the participants in the ontology engineering process agree with the output; then, the map is "translated" into an ontology, which is shared to facilitate feedback gathering (and possible modifications). The engineering process enrolled two ontologists and two clinicians (a physician specializing in clinical nutrition and an expert dietitian with yearly MNT experience for diabetic patients). AgiSCOnt methodology has already been adopted to develop some ontology-based DSSs related to healthcare (e.g., Refs. [56–58]). The following subsections describe the ontology engineering process with AgiSCOnt, delving into the main features of the developed ontology. OnT2D ontology is publicly available online[1]: it is serialized in Turtle [59] and consists of 19 classes, 4 object properties, 56 datatype properties, and 30 individuals; the uploaded ontology presents the data of the patients addressed in this paper.

3.1. Domain analysis and conceptualization

The elicitation of relevant expert domain knowledge was performed utilizing unstructured interviews with the two clinicians. The interviews introduced the fundamental aspects of AgiSCOnt (cooperation, knowledge elicitation, conceptualization, testing) to increase the experts'

[1] OnT2D can be accessed here: https://www.stiima.cnr.it/wp-content/uploads/OnT2D.txt.

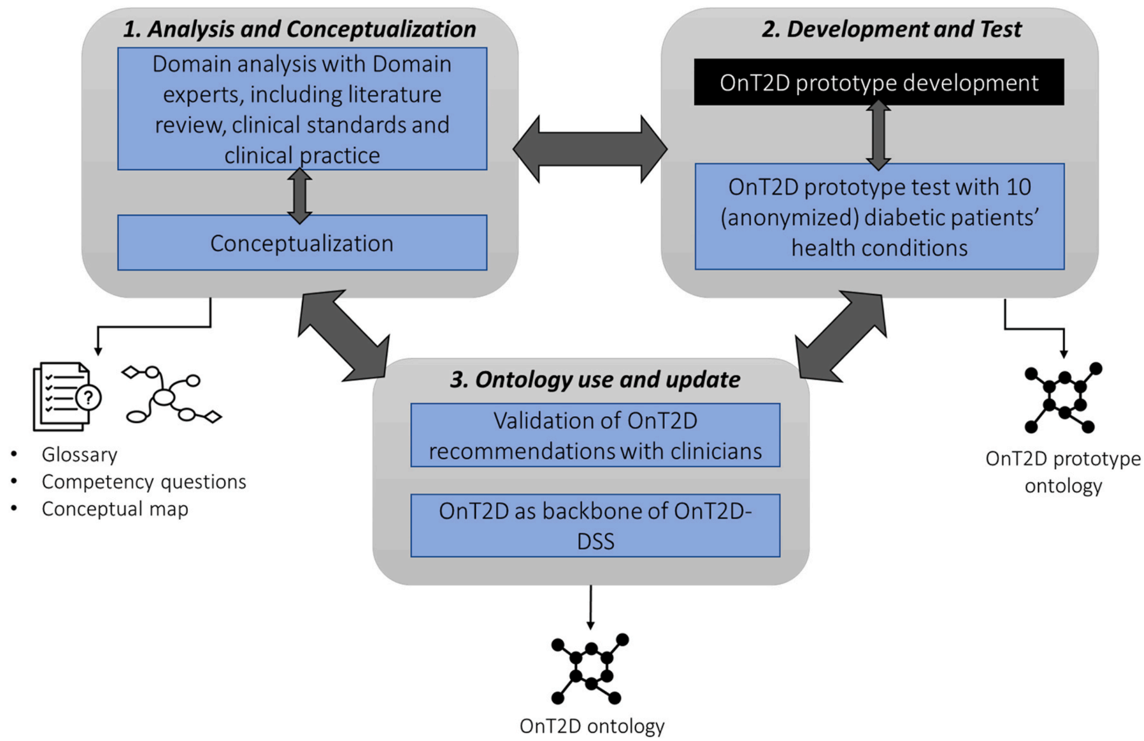

Fig. 1. AgiSCOnt's steps applied to OnT2D. The ontology engineering process begins with domain analysis and conceptualization, producing the Glossary, CQs, and the conceptual map as outputs. These outputs inform the development of the prototype ontology, which is tested against the conceptualization and ten health conditions. Once this step is concluded, the prototype OnT2D's MNT recommendations are validated with a team of clinicians (see also Section 4), and, thus, OnT2d is adopted as the "backbone" in OnT2D DSS. The public availability of the ontology enables the possibility to gather further feedback and foster the ontology's update, according to AgiSCOnt's instructions.

involvement in the ontology engineering process. Through discussions, the main concepts on the domain of MNT for T2D were elicited and conceptualized in a conceptual map (Fig. 2). Domain experts relied on their clinical experience to identify relevant knowledge, bearing in mind that general practice clinicians and family clinicians may not be able to rely on advanced techniques when visiting and receiving patients in their offices (for example, they cannot conduct bioimpedance measurement).

The map shows how the domain is centered on the patient and her/his health condition – characterized by blood tests' results and some fundamental parameters that any clinician can easily measure. The health condition can then be classified according to an anthropometric phenotype derived from the patient's Body Mass Index (BMI, obtained leveraging the patient's weight and height). Considering the multi-morbidity characterizing patients (in particular, older ones), *kidney failure* and *sarcopenia* where selected as comorbidities to be represented (besides the presence of pre-diabetes or T2D) since they can significantly impact MNTs. From a clinical perspective, these two morbidities' presence (or absence) is relevant and, therefore, should be explicit. Patient's health conditions are characterized by a set of data that are acquired via blood works or urine tests and that are *necessary* to enable the clinical analysis of a T2D status (Low Density Lipoprotein (LDL), Glycated Hemoglobin (GHb), albuminemia, triglycerides, High Density Lipoprotein (HDL)) and kidneys' status (microalbuminuria). Also, health conditions are completed with the patient's specific anthropometric measurements (weight, height, calf circumference) and an estimation of the Physical Activity Level (PAL). The measurement of calf circumference was selected since it is a more convenient way to assess the sarcopenic status of a patient rather than adopting more elaborate techniques [60].

The MNT recommendations inferred by the ontology are also characterized by a set of measurements related to caloric intake and micro- and macro-nutrients. The recommended *caloric intake* is calculated relying on the two couples of equations by Mifflin St.-Jeor and Harris-Benedict, depending on the patient's anthropometric phenotype. Carbohydrates, proteins, and lipids are calculated as a percentage of caloric intake, indicating each nutrient's minimum and maximum amounts. Following local guidelines for T2D management, maximum amounts for cholesterol, sodium, and alcohol were set. Fiber is paramount in the glycemic control for T2D patients [61] and should be calculated depending on the caloric intake. Lipids rates in T2D MNT can vary depending on the patient's specific health condition. The knowledge regarding specific nutrients and their definitions is summarized in Table 2 (glossary).

Based on the BMI value, six anthropometric phenotypes were identified: underweight (BMI <18.5), normal weight ($18.5 \leq$ BMI ≤ 24.9), overweight ($24.9 <$ BMI ≤ 29.9), obese I type ($29.9 <$ BMI ≤ 34.9), obese II type ($34.9 <$ BMI ≤ 39.9), and obese III type ($39.9 <$ BMI ≤ 44.9). For each phenotype, domain experts compiled a set of rules to determine the rates and amounts of micro- and macro-nutrients, following the Italian guidelines for MNT for T2D patients [62,63] and integrating the knowledge with anthropometric- and health condition-specific notions [64,65]– reported in Appendix B.

This step also produced a set of CQs (Appendix A), which is used to evaluate the ontology. Following AgiSCOnt's steps, one domain ontology was identified (from scientific literature [39]) as suitable for reuse – the Diabetes Diagnosis Ontology (DDO) [66], further extended into Diabetes Mellitus Treatment Ontology (DMTO) [67]. However, considering that T2D revolves around a different purpose, the authors decided to rely on domain experts' knowledge and to map OnT2D's entities to DDO and DMTO's.

3.2. Development and test

The knowledge acquired and conceptualized during the previous step is formalized with OWL 2 DL [68] using the Protégé [69] ontology editor.

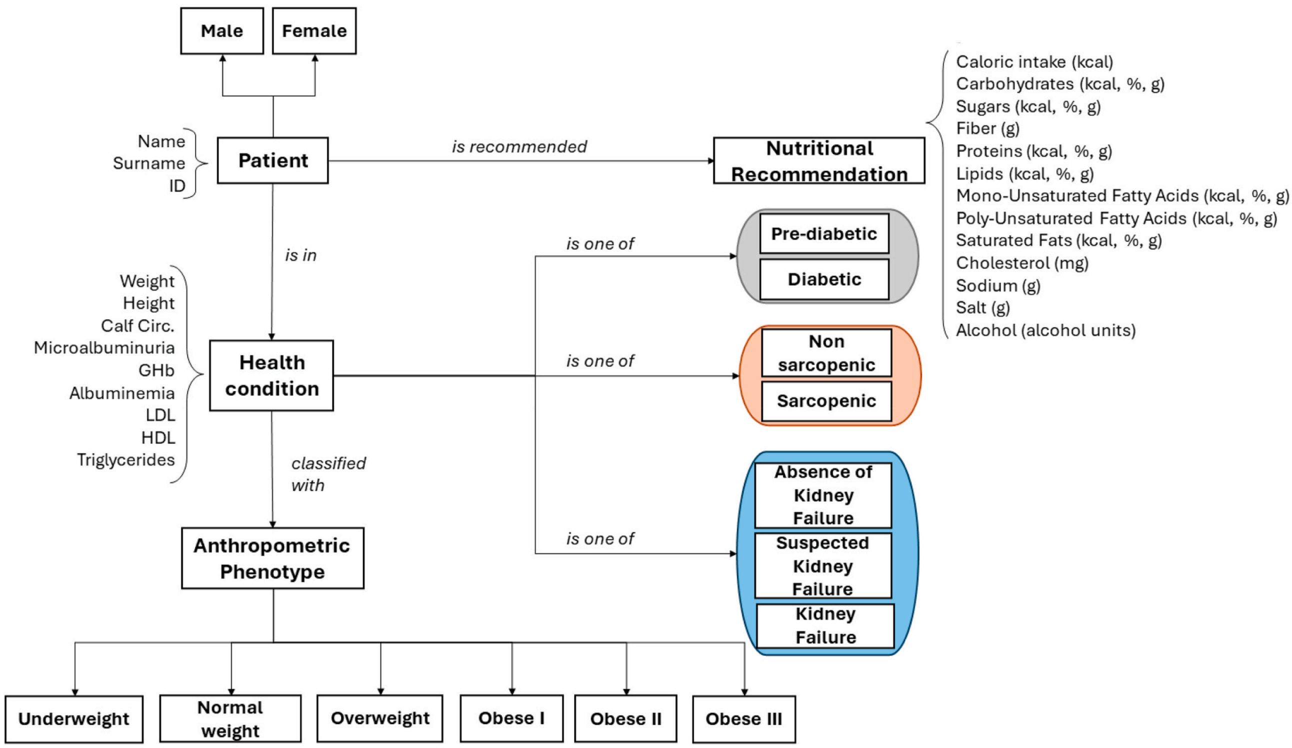

Fig. 2. The conceptual map drafted with clinical experts at the end of the Domain analysis and Conceptualization step. Main concepts are represented as rectangles, while arrows indicate relationships among concepts. Morbidities and their characterizations are represented as colored rounded rectangles. Curly brackets contain indications of the parameters clinicians deemed essential to identify a concept.

In this step, clinical experts are involved at the end of the development to evaluate whether the developed model accurately represents their take on the domain or if it requires further integrations. OWL 2 DL was selected as a suitable profile for engineering OnT2D, since this profile is expressive enough to model the entities and rules necessary. Entities are prefixed ont2d:.

The concepts pertaining to the patient and his/her health conditions were modelled as owl:classes. In particular, a ont2d:HealthCondition can be further specified (rdfs:subclassOf) as ont2d:Diabetic or ont2d:Pre-diabetic (which are disjointed), ont2d:Sarcopenic or ont2d:Non-sarcopenic (also disjointed), and ont2d:KidneyFailureAbsence or ont2d:SuspectedKidneyFailure or ont2d:KidenyFailure (also disjointed). In this way, a patient's health condition can be either in one or no one of the three conditions characterizing OnT2D patients. Moreover, subclasses of ont2d:HealthCondition are further described by means of owl:restrictions: for example, ont2d:SuspectedKidneyFailure is defined as.

Similarly, the ont2d:Anthropometric_Phenotypes concepts were represented as restricted subclasses on the datatype property ont2d:hasBMI. Fig. 3 illustrates the class hierarchy of OnT2D.

The ontology TBox is completed with a set of object properties relating patients to their health conditions (ont2d:hasHealthCondition) and MNT recommendations (ont2d:hasRecommendation) and their owl:inverseOf properties. Also, numerical values describing the health condition and the characteristics of the MNT recommendation are modelled as datatype properties. These properties (depicted in Fig. 4) provide fundamental parameters for the identification of comorbidities, diabetic and pre-diabetic conditions, sarcopenia, kidney failure, and anthropometric phenotype; furthermore, datatype properties are essential for listing and presenting the set of micro- and macro-nutrients rates and amounts necessary to provide a MNT recommendation.

The set of rules identified in the previous steps by clinical experts to determine the shares and amounts of nutrients for MNT recommendations were developed via Semantic Web Rule Language (SWRL) rules [70], a rule language flexible enough to enable the representation of equations. For example, the patient's BMR is calculated relying on the Harris-Benedict (1, 2) and Mifflin-St.-Jeor (3, 4) equations:

$$BMR_{female} = 655 + (9.56 \times weight\ (kg)) + (1.85 \times height\ (cm)) - (4.68 \times age\ (years)) \tag{1}$$

$$BMR_{male} = 66.5 + (13.75 \times weight\ (kg)) + (5 \times hieght\ (cm)) - (6.78 \times age\ (years)) \tag{2}$$

$$BMR_{female} = -161 + (10 \times weight\ (kg)) + (6.25 \times height\ (cm)) - (5 \times age(years)) \tag{3}$$

$$BMR_{male} = 5 + (10 \times weight\ (kg)) + (6.25 \times height\ (cm)) - (5 \times age(years)) \tag{4}$$

The adoption of Harris-Benedict or Mifflin-St.-Jeor's equations is determined by the patient's BMI: if the patient is affected by obesity, (3) and (4) are deemed more suitable for BMR estimation [71]. These conditions are represented via SWRL rules and adopted to determine a patient's BMR. The following rule represents equation (2) for the estimation of the BMR for a normal-weight male:

Male(?p), hasHealthCondition(?p, ?hc), hasBMI(?hc, ?bmi), lessThanOrEqual(?bmi, 29.9), hasYears(?p, ?y), hasHeight(?hc, ?h), hasWeight(?hc, ?w), multiply(?hby, ?y, 6.78), multiply(?hbh, ?h, 5), multiply(?hbw, ?w, 13.75), subtract(?hbs, ?hbh, ?hby), add(?hbf, ?hbw, 66.5), add(?BMR, ?hbf, ?hbs) → hasBMR(?hc, ?BMR)

Adopting a similar approach, the knowledge (recommendations and rules) developed by clinical experts during Step 1 (reported in Appendix B) has been represented as SWRL rules. For example, the identification of ont2d:Sarcopenic health conditions relies on SWRL rules confronting health condition's data with parameters defined by the domain experts:

Male(?p), hasHealthCondition(?p, ?hc), hasAdjustedCC(?hc, ?adjustedCC), lessThanOrEqual(?adjustedCC, 34.4) → Sarcopenic(?hc)

Table 2
A glossary of the main terms identified by domain experts to describe T2D patients.

Concept	Abbreviation	Description
Pre-diabetes and T2D terms		
Glycated hemoglobin	GHb	can be used to identify T2D in a patient; it is a convenient method that does not require special preparation, such as fasting; measured in mmol/mol.
Basal Glycemia	BG	a.k.a. “basal blood glucose”, is an estimation of blood glucose level after a 9-h fast; measured in mg/dl.
Post Prandial Glycemia	PG	blood glucose as measured after a meal; measured in mg/dl.
Impaired Fasting Glucose	IFG	risk factor for developing the disease and it represents a necessary condition for classifying a patient as pre-diabetic; measured in mg/dl.
Impaired Glucose Tolerance	IGT	estimated 2 h after oral glucose load; with IFG and GHb, it is a necessary condition to assess pre-diabetes.
Metabolic and progression terms		
Albuminemia	–	concentration of albumin plasma protein; measured in g/dl.
Microalbuminuria	–	level of albumin found in urine sample; measured in mg/die.
Health condition terms		
Pre-diabetes	–	condition characterized by levels of GHb between 42 and 47, IFG between 100 and 125, IGT between 140 and 199.
Type-2 Diabetes (T2D)	–	condition characterized by levels of BG higher than 126 or GHb level higher than 48
Non-sarcopenic	–	absence of a progressive decline of muscle mass.
Sarcopenic	–	condition of progressive decline of muscle mass. It can be assessed leveraging CC and BMI (according to Ref. [60]).
Kidney failure	–	a.k.a. “renal failure”, is a condition in which kidneys are unable to filter and clean blood. Assessed when microalbuminuria levels are equal or greater than 300.
Suspected Kidney failure	–	condition characterized by microalbuminuria levels between 30 and 299.
Kidney failure absence	–	condition in which kidneys regularly perform blood filtering and cleaning activities.
Anthropometric phenotypes-related terms		
Body Mass Index	BMI	ratio between a patient’s weight (in kg) and the square of height (in m); calculated in kg/m^2.
Body Mass Fat Index	BMFI	ratio between a patient’s weight (in kg) and the square of height (in m), representing an alternative estimate of body composition; calculated in kg/m2
Fat Free Mass Index	FFMI	Ratio between a patient’s weight (in kg) and the square of height (in m), representing an alternative estimate of body composition; calculated in kg/m2
Hand grip	–	maximum voluntary muscle strength exerted by a patient’s hand; measured in kg.
Calf Circumference	CC	a patient’s circumference of his/her calf; measured in cm.

Female(?p), hasHealthCondition(?p, ?hc), hasHG(?hc, ?hg), lessThan(?hg, 20), hasBMFI(?hc, ?bmfi), greaterThan(?bmfi, 3.9), lessThan (?bmfi, 11.82), hasFFMI(?hc, ?ffmi), lessThan(?ffmi, 15) → Sarcopenic (?hc)

Also, the recommendations are formulated with rules. For example, given a patient with a suspect of kidney failure, the caloric intake from proteins recommendation is provided taking into account 90 % of the patient’s weight. This recommendation is independent from the phenotype:

Patient (?p), hasRecommendation(?p, ?r), hasHealthCondition(?p, ?hc), HealthCondition(?hc), hasWeight(?hc, ?w), hasMicroalbuminuria(?hc, ?malb), greaterThanOrEqual(?malb, 30), lessThan(?malb, 300), multiply(?prot, ?w, 0.9, 4.0) → maxKcalProteins(?r, ?prot)

A total of 19 classes, 4 object properties, 56 datatype properties, and 97 SWRL rules were modelled to adequately represent the knowledge necessary to classify health conditions and provide tailored MNT recommendations.

The OnT2D prototype was then tested, following AgiSCOnt’s instructions, against a set of use cases to check that the relevant knowledge was correctly represented within the ontology and that the inferences drawn were correct. To this purpose, clinical experts provided 10 male and female real and anonymized patients’ health conditions (using a k-anonymization approach [72], which ultimately suppressed the patients’ direct identifiers and replaced them with conventional IDs to mask the identity of the patients [73]) covering every phenotype and the conditions related to sarcopenia, kidney function, dyslipidemia, and triglycerides. For each patient, a set of MNT recommendations is inferred and discussed with domain experts to assess the correctness of the inferences. The recommendations provided by OnT2D were deemed correct and adequate for each patient. The OnT2D ontology is tested with the Pellet reasoner [74] – capable of treating SWRL rules – and the snapSPARQL plugin for Protégé ontology editor [75] to query the ontology and its materialized inferences. Moreover, to facilitate the use of OnT2D as a semantic layer for an application, the developed ontology was also tested with the SL reasoning type of the Stardog Enterprise RDF triple-store (also supporting both OWL 2 DL and SWRL rules) [76].

The inferences drawn for each patient were evaluated as correct, both those pertaining to the classification of the patient’s health conditions and those related to the MNT. However, clinical experts recommended adding an “alert message” for patients affected by suspected kidney failure to support family clinicians in promptly identifying such conditions. An SWRL rule was therefore added to OnT2D:

Patient(?p), hasHealthCondition(?p, ?hc), SuspectedKidneyFailure(?hc) - > medicalWarning(?r, “Risk of kidney damage - nephrological visit strongly recommended"^^xsd:string)

This rule, together with the owl:restriction on the ont2d:SuspectedKidneyFailure described above, enables the materialization of the string within the patient’s recommendation.

Finally, OnT2D was checked with the Ontology Pitfall Scanner (OOPS!) [77] before its use to identify the presence of common pitfalls (e.g., synonymic classes, miseuses of “is-a” relationship, properties not defined correctly, loops, etc.). The test run on OnT2D did not report any pitfall among those retrievable with OOPS!

The following Fig. 5 sketches a “patient journey”, indicating the input (health data) required for the ontology to reason and exemplifying some of the recommendations generated. The clinicians’ feedback regarding the recommendation depicted here is discussed in the following Section 4.1.

3.3. Ontology use and updating

Following the development step, AgiSCOnt foresees the dissemination of the developed ontology to foster its refinement and reuse. To this extent, the ontology is published online and disseminated to other stakeholders via domain experts and ontologists in order to obtain feedback. Feedback acquisition is essential to increase OnT2D shareability, especially if the ontology is adopted as the backbone of a digital application.

A prototypical application of the OnT2D ontology – the OnT2D-DSS – was developed to allow the acquisition of feedback from general practice doctors (as detailed in Section 5). The prototype was developed in

```
owl:equivalentClass [ rdf:type owl:Restriction ;
                      owl:onProperty ont2d:hasMicroalbuminuria ;
                      owl:someValuesFrom [ rdf:type rdfs:Datatype ;
                                           owl:onDatatype xsd:integer ;
                                                     owl:withRestrictions
                                                    ([xsd:minInclusive 30]
                                                   [xsd:maxExclusive 300])
                                         ]
                     ] ;
                     rdfs:subClassOf ont2d:HealthCondition .
```

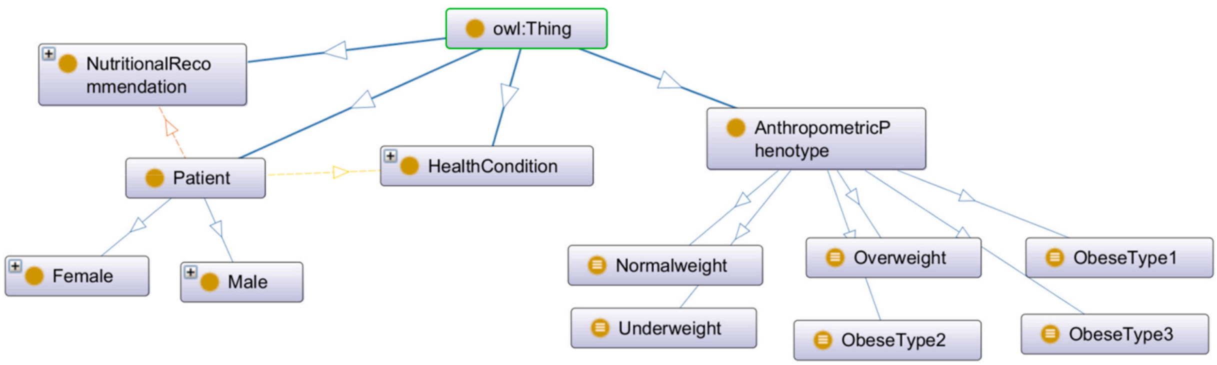

Fig. 3. The hierarchy of classes (with a focus on ont2d:AnthropometricPhenotype and its subclasses) for OnT2D.

Python and leverages the Owlready2 package[2] to interface with the underlying ontology (OnT2D), add new instances, and perform reasoning to obtain personalized recommendations, while the simple graphical user interface was devised using the Streamlit open-source framework.[3] Fig. 6 shows the OnT2D-DSS's main interface a family doctor has access to, including the input fields to add patient's information (e.g., general information such as gender and age; phenotypical data such as BMI, PAL, and CC; metabolic data acquired via blood works and tests, such as albuminemia, microalbuminuria, LDL, and triglycerides). Moreover, by clicking on the "Get recommendations" button, the doctor can retrieve the tailored MNT recommendations for the patient (Fig. 7). For the sake of simplicity, the recommendations pertaining to the patients selected for the preliminary validation (see Section 5) are pre-loaded as text files in OnT2D-DSS. In this way, family physicians can validate the application more efficiently. The resulting application runs locally on a laptop and supports two languages, namely Italian and English (the application's Graphical User Interface is represented in the Supplementary M*aterials I* file).

The OnT2D-DSS prototype, developed as a desktop application, contains the recommendations generated by the ontology for each of the 10 patients. The prototypical application – developed purely as a test to receive general practice doctors' feedback and insights – was developed in Italian.

4. Preliminary validation of OnT2D MNT recommendations

Since the clinical validity of MNT recommendations is pivotal, a validation experiment with clinical personnel was set up to validate the inferences generated by the ontology to increase the ontology's shareability. Therefore, the preliminary validation proposed for OnT2D is the same as that adopted for similar expert systems (e.g., Ref. [57]) and requires experts to assess the correctness and validity of the inferences provided by the ontology. For OnT2D, 11 clinicians (dieticians and clinical nutritionists operating in hospitals and with experience with T2D patients, not related to the domain experts participating in the ontology engineering process), practicing their profession for 4.5 years on average in different Italian clinics and hospitals, agreed to participate in the validation experiment.

4.1. Experiment methodology

Clinicians were provided with a brief document describing the experiment and its purpose, as well as the activity they were asked to partake in; they were also informed about the purpose of OnT2D. Participants were asked to evaluate a subset of the 10 real patients' health conditions modelled in OnT2D and the recommendations inferred by the ontology. Clinicians were provided with patients' *essential clinical information* (gender, age, BMI, CC, albuminemia, microalbuminuria, PAL, triglycerides, and LDL, as illustrated in Fig. 8) and with a *recommendation sheet* reporting the inferences drawn by OnT2D (anthropometric phenotype, kidney function, sarcopenia, dyslipidemia) (Fig. 9). The full list of patients' health conditions and the MNT recommendations generated with OnT2D and evaluated by the clinicians is available as S*upplementary materials II*.

Each participant was interviewed individually and was asked to evaluate the recommendations provided for each of the patients composing the subset (Table 3) ranging from "1 – Totally disagree" to "5 – Completely agree". Also, for each quantitative answer, participants were asked whether they wanted to motivate it, thus enabling the collection of secondary data (participants' observations, comments, and field notes raised during the administration of patients' *essential information* and *recommendation sheets*). Participants were allowed to make calculations to verify the inferred information's correctness and interact with the interviewers; for each patient, clinicians were given a maximum of 20 min to provide their answers.

4.2. Results and discussion

A total of 11 complete questionnaires (each containing 4 evaluations corresponding to the patients composing the subset) were collected. The results provided by each clinician (*cn*) for each patient's MNT

[2] https://owlready2.readthedocs.io/en/latest/intro.html.
[3] https://docs.streamlit.io/.

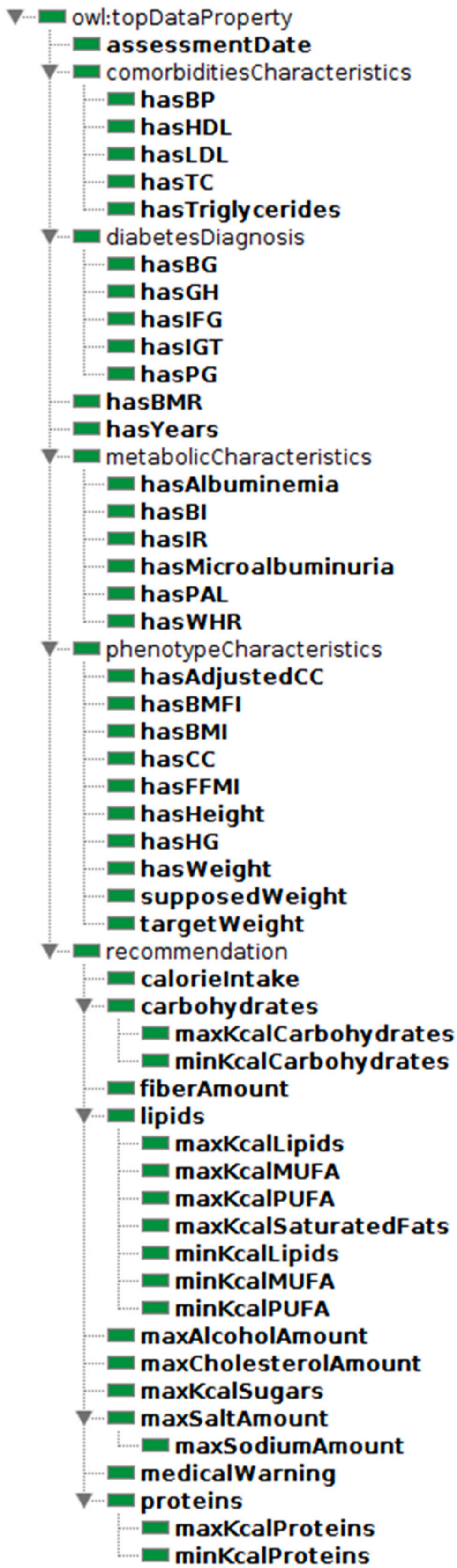

Fig. 4. The set of owl:datatypeProperty developed for OnT2D.

recommendation (P*n*) are reported in Appendix C. Fig. 10 summarizes the average (AVG) and standard deviation (SD) for each P*n*.

Also, some of the participants actively interacted with the interviewers (c2, c5, c7, c8, c11) with regard to some of the inferences drawn and to share their perspective on the usefulness of a system exploiting OnT2D. The comments are reported in Table 4.

The results reported above indicate that participants evaluated the inferences drawn by the system positively (more than 3.5). In particular, results are significantly closer to the maximum for patients P1, P2, and P6, while for patient P3 some concerns were raised. P3 was inferred to be a overweight diabetic patient with suspected kidney failure and sarcopenia – two major comorbidities. As indicated by clinical experts during the development of OnT2D, caloric intakes for overweight and obesity conditions are corrected according to the equation $CaloricIntake = BMR \times PAL - 500(kcal)$. As noted by c8 (Table 4), the caloric intake is adjusted taking into account both P3's PAL and the correction factor. A second concern related to P3 pertains her suspected impaired renal functions: for c2, before suggesting the caloric intake from proteins between 179 kcal and 201 kcal, further examinations on the patient's suspected kidney failure should be performed. However, as described in Section 3.2, OnT2D gives an "alert message" to family doctors for the prompt identification of these conditions. Also, the indication of a protein range and the "kidney damage alert" can support family doctors and general practitioners in selecting the lower bound until further examinations are concluded.

It is interesting to note that the results confirm the general correctness of the inferences generated with OnT2D and that the few generic comments provided by some participants during the experiment underline the role that this DSS may play in family doctors' work and patients' diet (comments from c2, c4, c8, and c11). Two clinicians (c5 and c7) provided comments regarding the possibility of adopting an Estimated Glomerular Filtration Rate to further assess a patient's renal function and regarding the possibility of further personalizing the diet for female diabetic patients in menopause, hinting also at the inclusion of cardiovascular diseases in the ontology. Two participants (c4 and c5) pointed out that the system may help family doctors to focus on nutrition – in this case, intended as MNT. Finally, the same two clinicians (c4 and c5) expressed the similarity between the results of their MNT recommendations and the ones provided by OnT2D.

5. Preliminary validation of the OnT2D-DSS with family physicians

Once the clinical validity of the inferences generated by OnT2D ontology is assessed, a second experiment took place to investigate the perceived ease of use of the OnT2D-DSS, its usefulness, and to gather feedback related to the potential intention to use such application and its relevance on the professional activities of family doctors.

5.1. Experiment methodology

To this aim, 5 family physicians (2 females and 3 males, located in the Lombardy Region, in Italy) were asked to interact with the OnT2D-DSS prototype. The participants' experience as family physicians ranged from 7 to 35 years, and the number of patients they care for varies between 1600 and 2100.

The clinicians were only informed of the purpose of the application – supporting them in providing T2D patients with tailored MNT recommendations – and interacted with the application using a laptop computer provided by the interviewers. To limit the duration of the experiment, 4 patients and their health conditions – selected by the two domain experts from the list of 10 patients used to validate the ontology (Section 3.3) – were uploaded in the DSS and the clinicians were able to see each of them – and the recommendations provided by the system. At the end of the interactions (which was set to a maximum of 15 min), each family doctor was administered five subscales of the Technology

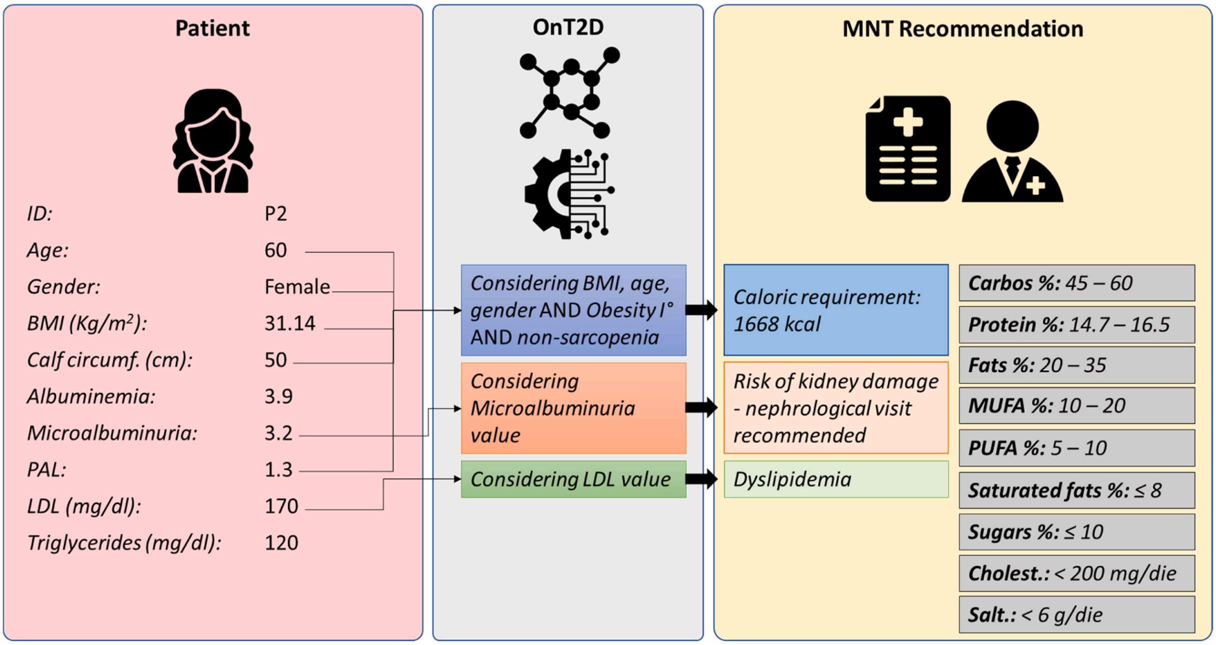

Fig. 5. An illustrative representation of the “patient journey”: health data composing the patient’s health condition are used by OnT2D to draw inferences, which compose the MNT recommendation. The reasoning process uses the rules described in this Section and in Appendix B to draw inferences pertaining to the comorbidities and tailored MNT recommendations, which the family doctor ultimately adopts as a guideline to support T2D patients.

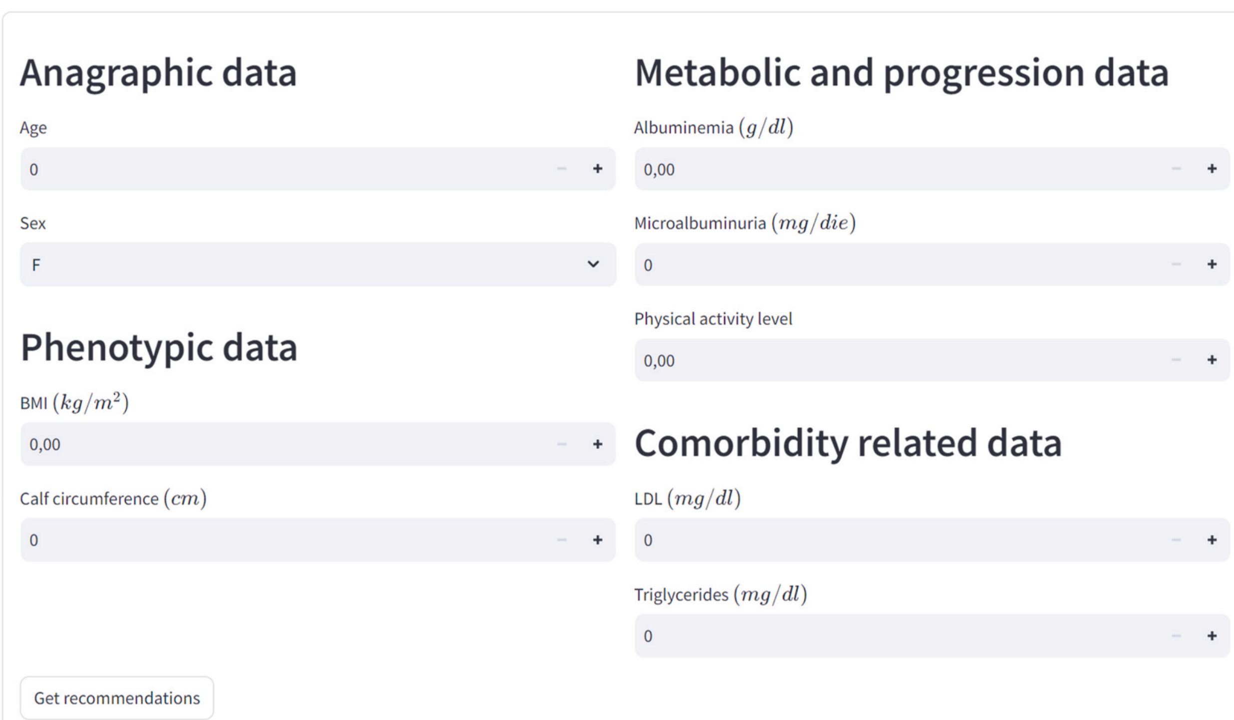

Fig. 6. The OnT2D-DSS interface, showing patient’s information and the “get recommendation” button (on the bottom-left corner).

Acceptance Model questionnaire (TAM3) [78]; the adoption of TAM3 subscales is common (particularly for digital applications, including DSSs) to investigate the degree of agreement for the perceived usefulness, the perceived ease of use, the extent to which the application actually does what it was designed to do, and the intention of use.

- Perceived Usefulness (PU), to assess the physicians’ believes that using OnT2D-DSS impacts on their professional performance;
- Perceived Ease of Use (PEOU), to investigate the perceived effort in using the prototype;
- Job Relevance (REL), to asses if the OnT2D-DSS is applicable to the family physicians’ job;
- Output Quality (OUT), to obtain clinicians’ judgement on OnT2D-DSS’s performance in providing MNT patient-tailored recommendations;

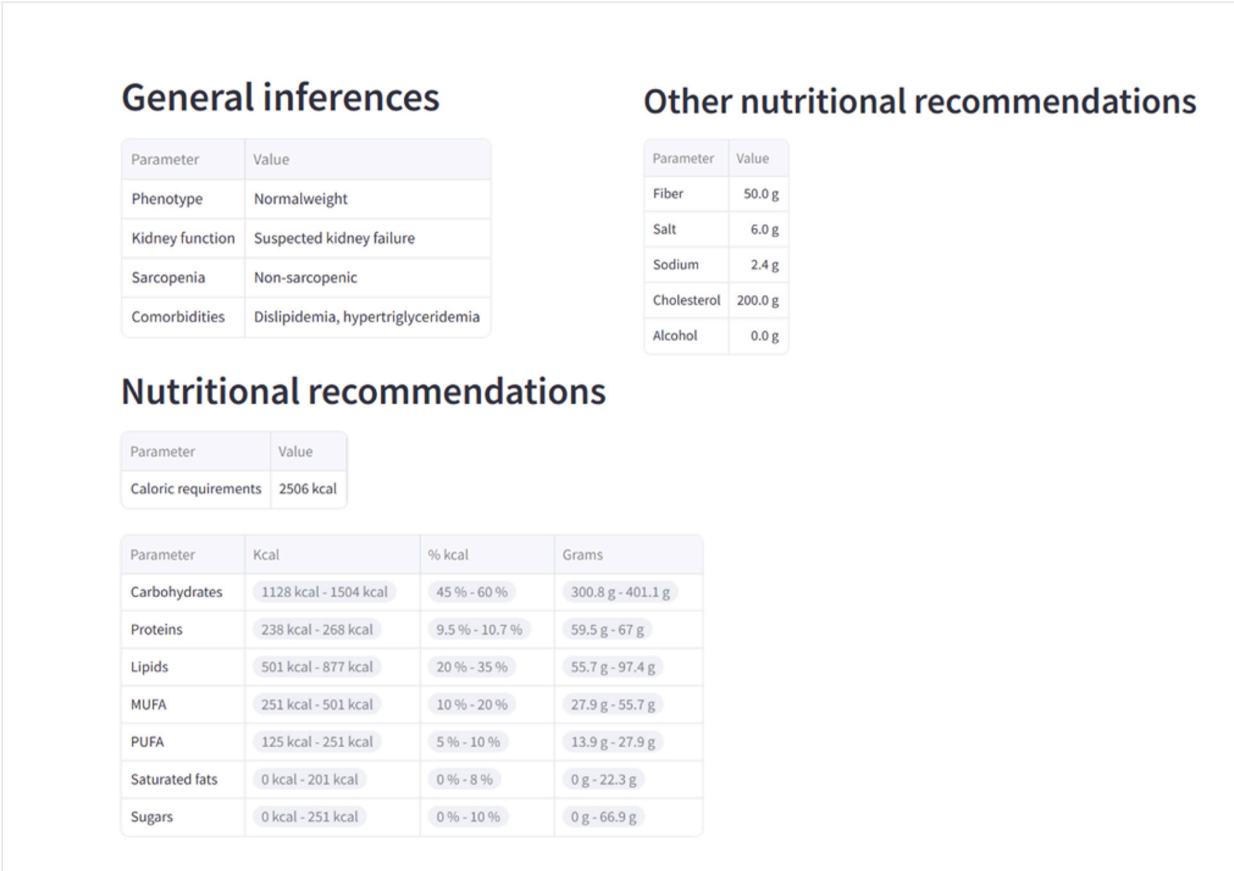

Fig. 7. The OnT2D-DSS interface illustrating the MNT recommendations performed based on the patient's data (reported in Fig. 6).

- Behavioral Intention (BI), addressing clinicians' availability to use OnT2D-DSS.

5.2. Results

For each of the sentences composing the subscales, the participants were asked to rate their degree of agreement (using a 5-point Likert scale ranging from "1 – Totally disagree" to "5 – Completely agree"). The quantitative results of the preliminary validation of the DSS with TAM3 are reported in Table 5.

For each subscale, the average value is $\geq$ 4.0, with no significant deviation among participants' opinions. Fig. 11 represents the average values for each of the TAM3 subscales investigated, with the aim of illustrating the aggregate results for PU, PEOU, REL, OUT, and BI.

After answering the questionnaire, participants were asked whether they wanted to make some spontaneous comments regarding OnT2D-DSS. The comments are reported in Table 6.

6. Discussion

The results from the preliminary validation of OnT2D and the DSS application (OnT2D-DSS) allow us to make some considerations. Concerning ontology, its validation indicates that OnT2D is capable of providing clinically plausible MNT recommendations for diabetic patients, including patients also affected by some comorbidities. In particular, the ontology was tested with 4 patients representing a variety of health conditions, and for all of the recommendations generated for the patients, participants' opinions were positive – although some aspects related to recommendations pertaining to kidney functions could be revised. In detail, following Step 3 of AgiSCOnt, the results of the experiment can also be considered as a way to further elaborate the knowledge underlying the ontology to include a more comprehensive and exhaustive representation of kidney functions and their impairments. Albeit the current version of OnT2D conforms to clinical standards regarding the definition of kidney failure and suspected kidney failure, the ontology can always be enriched with additional datatype properties to describe parameters adopted to identify renal impairments: in the case of the inclusion of the Estimated Glomerular Filtration Rate as a parameter for assessing kidneys functionality, this information could provide further insights on the patient's conditions, thus supporting family doctors and general practice clinicians in defining an appropriate MNT. Regarding the possibility of extending OnT2D's domain to cardiovascular diseases (as pointed out also by one family clinician, Table 6) and menopause, it would require the involvement of different clinical domain experts: this aspect is foreseen by the OEM adopted and might impact some of the rules already identified (for example, for female diabetic patients it would be necessary to understand how menopause impacts on the dedicated recommendations and modify the existing SWRL rules).

With regard to the participants' perceived usefulness of a clinical DSS adopting OnT2D, the quantitative data are supported by a limited amount of secondary data sources – comments spontaneously expressed by the clinicians during the interviews. However, the second experiment related to the preliminary validation of the prototype OnT2D-DSS underlined that the PU is significant (4.2/5). Although the sample of participants is limited, the preliminary results indicate that an OnT2D-DSS could be perceived as a valuable tool to support family doctors in managing MNT for T2D patients. This claim is also underlined by the positive results scored in the items pertaining to Job Relevance (REL) and Behavioral Intention (BI), which underlined family clinicians' interest in the proposed system.

In particular, OnT2D-DSS seems to be appreciated for the support it

Personal data	
ID	P1
Age	35
Gender	M

Phenotype data	
BMI (kg/m^2)	24.33
Calf Circumference (cm)	41

Metabolic data	
Albuminemia (g/dl)	4.3
Microalbuminuria (mg/die)	40
Physical Activity Level (PAL)	1.45

Comorbidity-related data	
LDL (mg/dl)	180
Triglycerides (mg/dl)	250

Fig. 8. The essential clinical information pertaining the patient.

Table 3
The sample of patients adopted for the evaluation of OnT2D inferences by clinical experts.

Patient ID	Characteristics
P1	Male, 35 years, normal weight, non sarcopenic, dyslipidemia, high triglycerides level, suspected kidney failure
P2	Male, 60 years, type 1 obesity, non sarcopenic, dyslipidemia, suspected kidney failure
P3	Female, 57 years, overweight, sarcopenic, suspected kidney failure
P6	Female, 61 years, overweight, sarcopenic, dyslipidemia

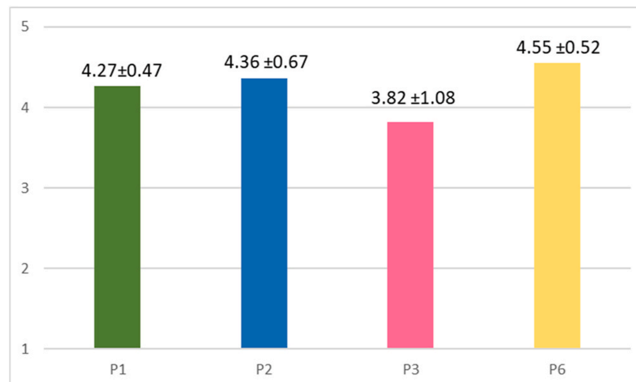

Fig. 10. A graphical representation of the evaluations provided by the clinicians for each of the proposed patients (P*n*); average and standard deviation values are also reported for each patient.

General recommendations inferred	
Phenotype	Normal weight
Renal function	Suspected kideny failure
Sarcopenia	Non sarcopenic
Comorbidities	Dyslipidemia, elevated triglycerides

MNT recommendations (Kcal, %, g)						
Caloric intake	2506 Kcal					
	min (kcal)	**max (kcal)**	**min (%)**	**max (%)**	**min (g)**	**max (g)**
Carbohydrates	1128	1504	45	60	300,8	401,1
Proteins	238	268	9.5	10.7	59,5	67,0
Lipids	501	877	20	35	55,7	97,4
MUFA	251	501	10	20	27,9	55,7
PUFA	125	251	5	10	13,9	27,9
Saturated fats	--	201	--	8	--	22,3
Sugars	--	251	--	10	--	66,9

MNT recommendation (quantities)	
Fiber	**max (g)** 50
Salt	**max (g)** 6
Sodium	**max (g)** 2.4
Cholesterol	**max (mg)** 200
Alcohol	**max (alcohol units)** 0

Fig. 9. The MNT recommendations inferred for the patient.

Table 4
Secondary data gathered from participants. General comments dedicated to the whole system are not attributed to any patient (–).

Clinician	Patient	Comment
c2	P3	"caloric intake from proteins might be too high: renal function should be checked completely" … "I think it could facilitate general physicians' work to some extent"
c4	P1, P3	"the program did what I would have recommended for this patient" … "(the system) relies on the same knowledge I use in my work as dietician"
c5	P2, P3	"it could be interesting to include the Estimated Glomerular Filtration Rate as a parameter to assess renal function" … "I can understand and agree with the system's decisions" … "it (the system) helps family doctors to focus also on a field they usually neglect (nutrition)"
c7	–	"menopause could be considered in the system, since it is a risk factor for cardiovascular diseases, which could impact on MNT"
c8	P3	"caloric intake for this patient seems to be too low, but it might be because of the correction of BMR"
c11	–	"this (system) could be useful for family doctors with older diabetic patients" … "it could save both clinicians and patients some time" … "it would be interesting to get patient's feedback on the recommended diet after a period of time"

provides to general practice clinicians in overcoming the lack of preparation in this field – also considering that MNT is generally neglected in clinical practice (as reported in Refs. [79,80], and also as highlighted in the comments reported in Table 6). While local national guidelines are essential and generalist strategies for the immediate and day-to-day management of T2D, a tool capable of tailoring MNT according to patient's specific characteristics could significantly improve the quality of the therapy – and possibly foster better results. The simple interface characterizing the OnT2D-DSS prototype resulted in significant scores in the Perceived Ease of Use (PEOU) and, consequently, in Output Quality (OUT): the minimalistic graphics and easy-to-grasp results were appreciated by all the family clinicians involved in the second experiment (Table 5).

It could be argued that the perceived usefulness of OnT2D-DSS in supporting general practice clinicians could also be motivated by their current working conditions. It is no novelty that, following the COVID-19 pandemic, family clinicians are facing an increase in the number of patients [81] (which is also confirmed by the number of patients the five family doctors reported during the second experiment). In such conditions, the participants' difficulty in focusing on granting patient-tailored nutritional advice emerged (Table 6).

It is also interesting to observe that the experiment provided a collateral result that endorses the domain experts-based approach: OnT2D was developed relying on clinical expert knowledge. This aspect enabled the clinicians involved in validating the inferences generated by OnT2D to transparently evaluate the majority of the recommendations provided by the system – some also commented that inferences drawn by the ontology were the same as they would have made. The fact that ontology's reasoning based on "if-then" rules somehow resembles human reasoning capabilities is fundamental to ensure OnT2D transparency [47] – it is not by chance that a large portion of nutrition recommendation systems adopt this type of rule [82]. Moreover, by adopting tableaux reasoners (such as Pellet), which are able to generate the list of predicates to move from the premises to the conclusions (proofs), it is possible to illustrate the reasoning process to end users. In this way, it would be possible to take some steps towards xAI and start relaxing the entrenched reluctance characterizing clinical personnel in adopting digital and AI-based technologies [83].

7. Limitations

The proposed DSS and its underlying ontology present some limitations that need to be addressed.

While the collaborative approach underlying the development of OnT2D can provide a (partial) solution to the reluctance to adopt AI-based systems in clinical practice, the efforts related to its development and maintenance are significant. The collaborative approach needs to include a considerable – yet manageable – number of domain experts and stakeholders in the ontology engineering process to ensure the model's shareability: in this way, the semantic representation and the inferences it generates can be perceived as reliable [48]. In the case of OnT2D engineering, the development team was limited to four collaborators, while the inferences generated were assessed by a different pool of experts (as described in Section 4). Again, if such a process can support the ontology's shareability, it requires access to many domain experts.

Automation can support the engineering process [84], but it must be accounted for – so as not to incur the "black box" lack of transparency issue. With regard to the explainability of AI, although the research efforts in the field of xAI marked significant signs of progress, the role of ontologies in such a context pertains to the symbolic approach: as pointed out in some recent works [85], knowledge-based approaches can enormously benefit from the combination with neural approaches, as they would add the ability to learn to ontologies' ability of reasoning about what is learned. Therefore, OnT2D ontology could be potentially combined with data-driven approaches dedicated to the investigation of

Table 5
The evaluation scores given by participants (doc1, …doc5) for each item composing the TAM3 subscales.

Item	Item sentence	*Doc1*	*Doc2*	*Doc3*	*Doc4*	*Doc5*	AVG	SD
PU1	Using the system improves my performance in my job.	3	5	4	4	5	**4.2**	**0.84**
PU2	Using the system in my job increases my productivity.	3	5	5	4	5	**4.4**	**0.89**
PU3	Using the system enhances my effectiveness in my job.	3	4	5	4	4	**4**	**0.71**
PU4	I find the system to be useful in my job.	4	5	5	4	4	**4.4**	**0.55**
PEOU1	My interaction with the system is clear and understandable.	5	5	5	5	5	**5**	**0.00**
PEOU2	Interacting with the system does not require a lot of my mental effort.	4	5	5	5	5	**4.8**	**0.45**
PEOU3	I find the system to be easy to use.	5	5	5	5	5	**5**	**0.00**
PEOU4	I find it easy to get the system to do what I want it to do.	4	5	5	4	5	**4.6**	**0.55**
REL1	In my job, usage of the system is important.	3	5	4	4	5	**4.2**	**0.84**
REL2	In my job, usage of the system is relevant.	3	5	4	4	4	**4**	**0.71**
REL3	The use of the system is pertinent to my various job-related tasks.	5	5	5	5	5	**5**	**0.00**
OUT1	The quality of the output I get from the system is high.	3	4	5	4	5	**4.2**	**0.84**
OUT2	I have no problem with the quality of the system's output.	3	5	5	5	5	**4.6**	**0.89**
OUT3	I rate the results from the system to be excellent.	3	4	5	4	4	**4**	**0.71**
BI1	Assuming I had access to the system, I intend to use it.	3	5	5	5	5	**4.6**	**0.89**
BI2	Given that I had access to the system, I predict that I would use it.	3	5	5	5	5	**4.6**	**0.89**
BI3	I plan to use the system in the next 5 months.	4	5	5	4	5	**4.6**	**0.55**

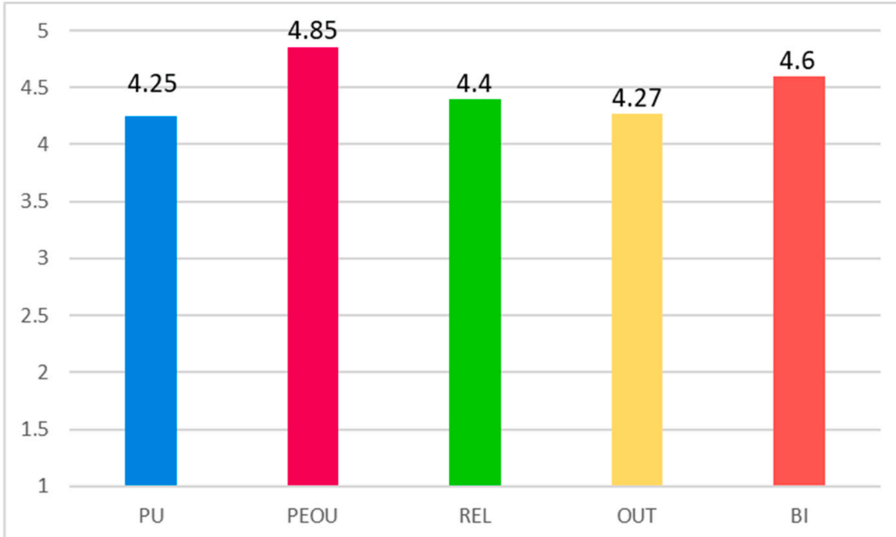

Fig. 11. A graphical representation of the aggregate evaluations (average values) for each of the TAM3 subscales adopted in this experiment (PU: Perceived Usefulness; PEOU: Perceived Ease of Use; REL: Job Relevance; OUT: Output Quality; BI: Behavioral Intentions).

Table 6
Secondary data gathered from the family doctors participating to OnT2D-DSS preliminary validation.

Clinician	Comment
Doc3, Doc4	"I have too many patients and it is almost impossible to offer personalized dietary indications to diabetic ones"
Doc1, Doc2, Doc3, Doc5	"Medical Nutrition Therapy for Type-2 diabetic patients is not a training topic for a family doctor"
Doc4	"This application is easier than many applications provided by the Region"
Doc4	"It [OnT2D-DSS] could be even more useful to consider other comorbidities, for example, gastro-enteric and cardiovascular diseases"
Doc4	"The decision support application is particularly useful for patients between 25 and 50, because it could increase their adherence to MNT since dietary prescriptions are personalized on their status"

different MNT approaches, T2D patients' dietary habits, and clinical recommendations. Nevertheless, research also needs to focus on explainability methods and metric – an issue involving researchers, institutions, and policy makers; some significant efforts towards explainability metrics have been made [86], including some attempts to unify multidimensional trustworthiness models [87]. In this regard, it is still premature for OnT2D (in its current purely symbolic form) to commit to any explainability method.

Although the preliminary results from both experiments are promising, the samples of participants (11 clinicians for the first experiment and 5 family doctors for the second) can only satisfy the minimum number of participants to grant preliminary considerations – according to Nielsen Norman Group [88]. Therefore, to strengthen the validation of the inferences generated by OnT2D, more tests with MNT experts from other samples are required. Similarly, further tests with a larger sample of general practice doctors need to be conducted to corroborate or controvert the preliminary results.

As highlighted by both experiments, there exist several other comorbidities that can afflict diabetic patients – cardiovascular diseases were mentioned twice (Tables 4 and 6). The possibility of increasing knowledge in OnT2D would require the involvement of different domain experts. However, this comment indicates a clear future research direction for improving ontology.

Finally, family doctors could interact with a prototype of the DSS application (OnT2D-DSS), providing positive evaluations. Although the authors are not expecting any considerable or massive modifications to its interface, it is worth noting that possible future changes may lead to different evaluation results.

8. Conclusions and future works

This work introduced OnT2D, a collaboratively engineered domain ontology for the MNT recommendations for Type-2 diabetic patients, and a prototypical application (OnT2D-DSS) devoted to supporting family doctors in providing diabetic patients with tailored nutritional recommendations. The paper's main contribution consists of the development of the ontology and the DSS application. The inferences generated by the ontology and the prototypical DSS application underwent a preliminary validation on two different samples of participants. The preliminary results collected with the two evaluations seem promising and encourage the further development of the ontology and the application. OnT2D-DSS underlines the role of clinical expert knowledge in supporting family doctors in managing T2D patients, highlighting how a "classical" approach could potentially enhance the MNT dedicated to these patients.

Nonetheless, the work on OnT2D is not yet complete. From an ontology perspective, as mentioned in Section 3.1, the domain model that has been developed needs to be mapped with existing ontologies. For this purpose, the Diabetes mellitus Diagnosis Ontology (DDO) [66] – and its extension DMTO [67] – could act as an upper model to align some of OnT2D concepts to DDO's ones, following an approach leveraged by other works [89]. Considering the possibility of including more comorbidities (following the feedback gathered from the preliminary validation phase), the OnT2D could also benefit from mapping its terms to a larger model (e.g., SNOMEDCT) to enhance its interoperability. Also, taking into account some of the suggestions obtained through the preliminary validation experiment, the possibility of further extending the comorbidities represented in the ontology will be investigated with the domain experts and extending the number of clinical experts involved in the ontology engineering process. To further corroborate the validity and correctness of OnT2D MNT recommendations for diabetic patients, a new experiment with another sample of dieticians is also desirable: this would confirm the preliminary results collected in the first experiment.

Similarly, with regard to the DSS application (OnT2D-DSS), other tests, including more family doctors (from different regions of the country), are required to confirm the preliminary results presented in this work. Moreover, family doctors could also be involved in a participatory effort to develop the final interface of the DSS to increase their willingness to adopt it and the perceived ease of use.

As mentioned in Section 6, the expert knowledge and ontological reasoning approaches enabled clinicians to understand (and interact with) the logic underlying OnT2D-DSS, enabling the possibility of acquiring (precious) feedback on several aspects of the ontology and the application. Nonetheless, a future development of the system should be able to integrate also inferences generated by (large) number of diabetic patients and their MNTs, thus contributing to enhancing the quality of the knowledge represented in the ontology (in line with AgiSCOnt's Step 3 for ontology maintenance and update).

With regard to the technological aspects, an effort needs to be performed to make the DSS operative; to this extent, the authors plan to rely on a middleware connecting the ontological layer to the application [90, 91], and to acquire patients' data (necessary for the elaboration of tailored MNT recommendations) from the Electronic Health Records available (at a national level, under the Electronic Health File [92]). Another promising data source worth investigating is the acquisition of physiological data from wearable devices designed for T2D patients. In a recent contribution, the effectiveness of such devices in managing glycemic levels was underlined [93]; moreover, technological advancements can foster the adoption of such data in clinical practice (e.g., with middleware capable of integrating data from heterogenous sources [94, 95]). Finally, since a pure ontology-based solution may result in a very large ABox (especially if this encompasses Electronic Health Records and data from wearables), an Ontology-Based Data Access architecture leveraging patients' data from relational databases may be a promising solution for the deployment of OnT2D-DSS on a large scale.

Finally, to foster feedback acquisition and disseminate OnT2D-DSS among clinicians, the findings of this research should be shared with clinical personnel and policy makers directly involved in managing diabetic patients. After OnT2D-DSS achieves a stable ontological layer and a finalized version of its interfaces, testing with family doctors and their patients could begin, thus providing valuable data to assess the application's usefulness in clinical practice.

CRediT authorship contribution statement

Daniele Spoladore: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Francesco Stella:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Martina Tosi:** Writing – original draft, Methodology, Investigation, Data curation. **Erna Cecilia Lorenzini:** Writing – review & editing, Validation, Supervision, Methodology. **Claudio Bettini:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix D. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2024.109001.

Appendix A. The list of CQs developed for the Domain analysis and Conceptualization phase of the ontology engineering process

CQ1	*Which information are required to identify a patient?* Each patient is represent with an ID (positive integer number), name, surname and other relevant data, such as the gender and age. Moreover, each patient is associated to a health condition.
CQ2	*What type of patients does the ontology consider?* The current version of the ontology takes into account Type-2 diabetic patients and pre-diabetic patients.
CQ3	*Which information characterize a patient's health condition?* The health condition of a patient is described by means of: A) blood tests results, which include albuminemia, microalbuminuria, Low Density Lipoprotein, High Density Lipoprotein, Glycated Hemoglobin, triglycerides; B) anthropometric data, including current weight, patient height, calf circumference; C) estimation of the Physical Activity Level
CQ4	*Which comorbidities are considered by this version of the ontology?* Sarcopenia and kidney failure are the two comorbidities considered by the ontology.
CQ5	*How is sarcopenia evaluated in the ontology?* Sarcopenia is evaluated via the value of the calf circumference together with the patient's BMI, following the rules reported in Ref. [60].
CQ6	*How is kidney failure evaluated in the ontology?* Kidney failure is assessed leveraging a patient's microalbuminuria level, according to clinical practice.
CQ7	*How is a MNT recommendation structured?* A recommendation must encompass: the adjusted daily caloric intake; the minimum and maximum caloric intake from carbohydrates; the amount of sugars; the amount of fibers; the amount and percentage of caloric intake from proteins; the minimum and maximum caloric intake from lipids; the minimum and maximum caloric intake from mono-unsaturated fatty acids; the minimum and maximum caloric intake from poly-unsaturated fatty acids; the maximum amount of cholesterol; the maximum amount of sodium; the maximum amount of alcohol.

Appendix B. The set of rules used to determine the rates and amounts of micro- and macro-nutrients, based on anthropometric phenotypes and health conditions

Appendix B.1. First part of the rules used to determine the rates and amounts of micro- and macro-nutrients, based on anthropometric phenotypes and health conditions

Phenotype	BMR	PAL	Caloric requirements	Proteins	Carbohydrates	Sugars	Fiber
Underweight	Harris-Benedict	1,45	BMR x PAL	0,9-1,2 g/kg BMI 18,5/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Underweight Sarcopenic	Harris-Benedict	1,45	BMR x PAL	0,9-1,2 g/kg BMI 18,5/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Normalweight	Harris-Benedict	1,45	BMR x PAL	0,9-1,2 g/kg/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Normalweight Sarcopenic	Harris-Benedict	1,45	BMR x PAL	0,9-1,2 g/kg/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Overweight	Harris-Benedict	1,45	BMR x PAL – 500 kcal	0,9-1,2 g/kg BMI 24,9/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Overweight Sarcopenic	Harris-Benedict	1,45	BMR x PAL – 500 kcal	1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity I°	Mifflin	1,3	BMR x PAL – 500 kcal	0,9-1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity I° Sarcopenic	Mifflin	1,3	BMR x PAL – 500 kcal	1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity II°	Mifflin	1,3	BMR x PAL – 1000 kcal	0,9-1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity II° Sarcopenic	Mifflin	1,3	BMR x PAL – 1000 kcal	1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity III°	Mifflin	1,3	BMR x PAL – 1000 kcal	0,9-1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die
Obesity III° Sarcopenic	Mifflin	1,3	BMR x PAL – 1000 kcal	1,2 g/target kg at 6 months/die	45–60 % tot kcal	<10 % tot kcal	20g/1000 tot kcal/die

Appendix B.2. Second part of the rules used to determine the rates and amounts of micro- and macro-nutrients, based on anthropometric phenotypes and health conditions

Phenotype	Lipids	Saturated Fats	MUFA	PUFA	Cholesterol	Sodium	Diet type	Alcohol
Non-obese phenotypes (sarcopenic and non-sarcopenic)	20–35 % tot kcal	<10 % tot kcal	10–20 % tot kcal	5–10 % tot kcal	<300 mg/die	<2,4 g/die (salt <6 g/die)	Low glycemic index, whole-grain foods	<10g/die females (1 unit) <20g/die males (2 units)
		if high LDL <8 % tot kcal			if dyslipidemia <200 mg/die			Abstention if triglycerides ≥150 mg/dL
Obese phenotypes (sarcopenic and non-sarcopenic)	20–35 % tot kcal	<10 % tot kcal if high LDL <8 % tot kcal	10–20 % tot kcal	5–10 % tot kcal	<300 mg/die if dyslipidemia <200 mg/die	<2,4 g/die (salt <6 g/die)	Low glycemic index, whole-grain foods	Abstention

Appendix C. Evaluation scores given by each participating clinician (c) to each patient-tailored recommendation (P)

	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	AVG	SD
P1	4	5	4	4	5	4	4	4	4	5	4	**4,27**	**0,47**
P2	4	4	5	5	3	4	4	4	5	5	5	**4,36**	**0,67**
P3	4	5	4	5	3	4	2	2	4	5	4	**3,82**	**1,08**
P6	5	5	5	5	4	5	4	4	4	5	4	**4,55**	**0,52**

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