

A Comprehensive Fuzzy Ontology-Based Decision Support System for Alzheimer's Disease Diagnosis

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ABSTRACT The World Health Organization (WHO) indicates that the proportion of the elderly will soon include nearly a quarter of the world population. Ensuring that health systems are prepared to deal with this phenomenal rate of aging and associated diseases generates many challenges. Among these challenges is facing Alzheimer's Disease (AD) that may occur at some point in the elderly life and may harm societies. AD is considered a neurological, psychological, mental, and health setback. The Clinical Decision Support System (CDSS) can improve patient care and support many medical functions, such as diagnosing diseases that can reduce preventable harm. This research's main objective is to design, implement, and evaluate the Alzheimer's Disease Diagnosis Ontology (ADDO). It is a comprehensive semantic knowledge base toward the development of fuzzy ontology-based CDSS for AD diagnosis. ADDO can serve as a core component of CDSS, which provides representation, annotation, and access to aspects related to AD's study and diagnosis. Toward the management of this objective, ADDO is based on the essentials of the Open Biomedical Ontology (OBO) and follows the Basic Formal Ontology (BFO) and the Ontology for General Medical Sciences (OGMS) principles. ADDO focuses on representing the patient characteristics, complications, drugs, diagnosis examination tests, and key aspects of their periodic visits in a standard way. The possibility of semantic interoperability is taken into account by integrating ADDO and a heterogeneous AD dataset. We used ADNI as a case study to mapping a set of real instances. To manage the medical domain's uncertainty, ADDO is extended to fuzzy ontology to accommodate the medical linguistic variables and enhance diagnosis results' efficiency. ADDO is constructed using Protégé 5.5.0 software and evaluated using the HermiT reasoner and SPARQL semantic queries. ADDO currently includes 7060 concepts, 99 properties, 46274 axioms, and 30708 annotations. As a result, ADDO is consistent and more reliable in managing most AD aspects than other existing AD ontologies.

INDEX TERMS Fuzzy ontology, clinical decision support system, Alzheimer's disease, knowledge based, Mild COGNITIVE impairment, ontology representation.

I. INTRODUCTION

Alzheimer's Disease (AD) is classified as a neurological disorder. It is associated with progressive damage to parts of the brain that are essential in forming memories and carrying out cognitive functions [1]. AD results in the death of neurons cells on a massive scale and significantly shrinking

brain tissue [2]. This negatively affects basic body functions, such as vision, swallowing, walking, and breathing. These patients need round-the-clock care. AD is a degenerative disease and ultimately fatal. Estimates from the World Health Organization (WHO), the current number of Alzheimer's patients has reached 36 million, and it is expected to reach 66 million patients in the world by 2030 [3]. AD is not a sudden event but a gradual process. Fig. 1 presents the gradual stages of AD. The most significant transition phase is called

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Mild Cognitive Impairment (MCI) [4]. These patients have cognitive function problems greater than normal age-related changes related to language, organizing, planning, memory, and judgment. To attract attention, MCI is one of the main indicators that allow early detection of AD to improve patients' quality of life. The most noticeable sign of AD diagnosis is memory impairment, followed by cognitive test domains. Besides, psychological and behavioral disturbances (delusions, depression, sleep changes, paranoia, wandering, and anxiety). The cause of AD is incompletely defined, and no truly effective therapy exists.

In general, early disease diagnosis may allow intervention to identify the underlying disease processes and thus modify or halt disease progression. As for AD, it may represent a significant challenge for many reasons [5]. First, oftentimes, friends or family members notice signs of MCI even before the patient realizes they have a problem. Second, current diagnosis approaches as markers for brain atrophy is not always present at early diagnosis. Third, the accumulation of amyloid plaques deposition that appears in the brain probably begins 10-15 years before the first sign of clinical impairment appears, followed by intracellular neurofibrillary tangles. Fourth, the appearance of some signs related to the characteristics of MCI (i.e., losing things often, changes in social behavior, depression, neuroticism, etc.). It may have other causes, such as medication side effects and certain psychiatric disorders.

When a primary care physician suspects MCI or AD, the patient is shown to a group of specialized doctors for further evaluation [6]: Geriatricians are specialized in studying body changes with age to see if the patient's symptoms indicate a serious problem. Geriatric psychiatrists can assess memory and thinking problems. Neurologists perform brain scans of the patient and review the presence of abnormalities for the brain and central nervous system. Neuropsychologists specialize in performing tests of memory and thinking.

AD is a serious and complex disease. So an exact medical evaluation is needed to define complete clinical instructions for the patient to make the appropriate diagnosis [7]. It includes patient demographic data, patient history (disease history, medical history, family history of AD or dementia), complications, drugs, and diagnosis examination test (physical examination, gene, MRI image, laboratory results, behavioral, and cognitive tests) [8]. Neglecting one of these clinical guidelines may lead to an incorrect diagnosis. This leads to great pressure on doctors to deal with various diagnostic elements in light of dealing with a large number of patient cases. Besides, the chronic nature of AD requires long-term care systems to meet the needs of the patients. So, the Clinical Decision Support System (CDSS) development, besides current emerging computational intelligence methods, can bring new directions for pushing medical care to success, especially for these serious diseases as AD.

One of the most critical operations in the medical domain is data sharing. But without the possibility of semantic interoperability among enormous medical data resources, sharing

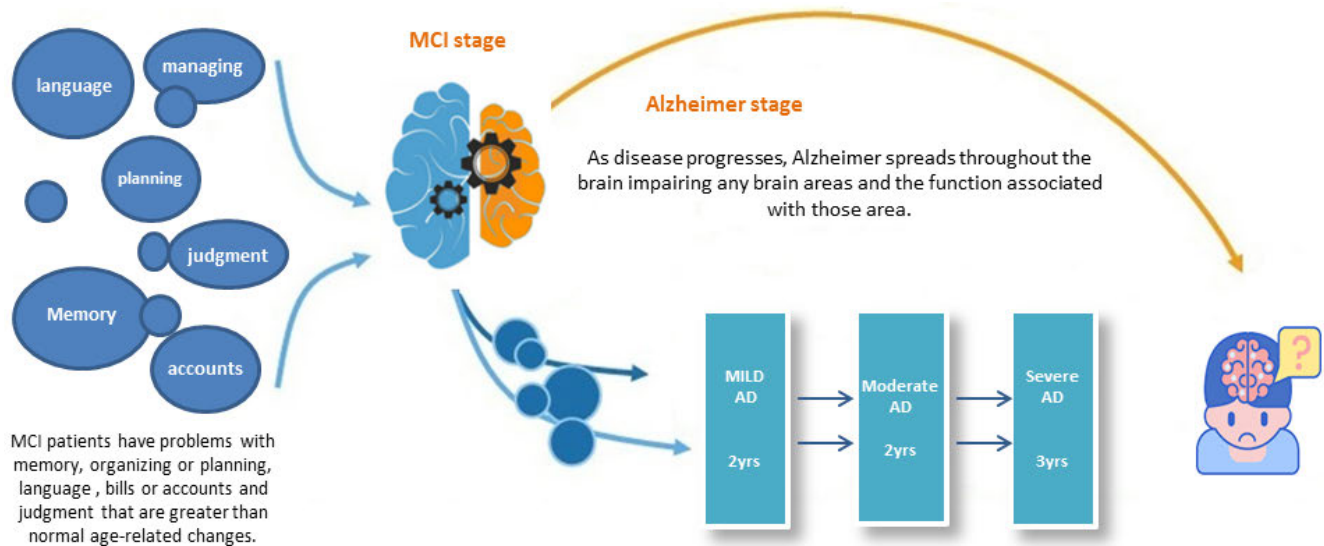
data in a meaningful way is unrealistic. It requires establishing a standardized structure for terms and relationships and describes their processes. The way to provide standardization is through building ontologies. Recently, there are more trends towards developing ontology-based CDSS models for highly specialized domains such as medical. Where ontologies development [9] is the critical step for modeling experts' knowledge. It plays a major role in knowledge management by enhancing the intelligence, efficiency and preserving the semantic interoperability of the CDSS [10].

Despite the success of ontologies in maintaining semantic relationships between their concepts, CDSS based on a crisp ontology cannot deal effectively with uncertainty or vague knowledge. This type of knowledge may not appropriate to deal with the difficult nature of the medical domain. To overcome these problems, Bobillo and Straccia [11] comprised fuzzy logic with an ontology using current languages and resources. Fuzzy ontology is an effective technology that significantly increases CDSS decision-making accuracy in real-world application domains.

Developing good ontology from scratch takes a lot of significant time and effort of ontology's authors [12]. So, ontology reuse allows for saving effort, time and guarantees a consistent representation of a specific domain. The starting point for developing a standard ontology is using Basic Formal Ontology (BFO) and Ontology for General Medical Sciences (OGMS) [13] as upper-level ontologies then reuse existing medical ontologies or terminologies, such as Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) [14], which is a multilingual vocabulary used for coding of clinical content (more than 300,000 medical concepts represented by an individual number). It is divided into several hierarchies as clinical findings, body structure, and biological product. It increases patient care efficiency by supporting the exchange of clinical terms, providing consistent representation, eliminating confusion, and improving data analysis.

BFO [15] developed by Barry Smith. Its goal is to make ontologies in a specific domain like biomedical have equivalent views on fundamental concepts, such as universals and particulars, time and space, and substances and qualities. It adopts a realistic approach into two disjoint categories of continuant (independent and dependent continuants, attributes, and locations) and occurrent (processes and temporal regions). OGMS [16] symbolizes the clinical entities in the disease and medical practice domain. It is useful in interpreting and recognition of the disease to improve healthcare.

Electronic Health Records (EHR) play a great role in monitoring and managing chronic diseases [17]. CDSS needs several data inputs to be processed. When CDSS integrates with the EHR, it gives CDSS an advantage to utilizing health management in real-time. One of the AD data sources available is Alzheimer's Disease Neuroimaging Initiative (ADNI) [18]. It is a longitudinal study designed to collect clinical, genetic, imaging, and biomarkers of MCI.



Alzheimer is not a sudden event but it is a gradual process. The most affected transition phase called Mild Cognitive Impairment (MCI), an intermediate stage between the normal age-related changes and the more serious decline of Alzheimer's disease.

FIGURE 1. The gradual stages of Alzheimer's disease.

The contributions of this research are as follows:

- 1) Provide the structure of the proposed ontology-based fuzzy CDSS model and discuss its sub-modules.
- 2) Develop a standard ontology as a knowledge base for AD patients (ADD0).
- 3) Ensure the semantic interoperability by integration between ADD0 and ADNI to enable patient mapping.
- 4) Implement and validate ADD0 for accuracy using the Protégé 5.5.0 tool.
- 5) Improve the way that crisp ADD0 is used to represent imprecise and linguistic information by extending ADD0 into the fuzzy ontology.
- 6) Compare ADD0 with existing ontology regarding the completeness reusability.

The rest of this paper is arranged in seven sections. Section 2 presents a review of related work that highlights the existing AD ontology. Section 3 introduces our approach as the ontology-based fuzzy CDSS, which supports physicians in their AD diagnosis decision-making. Section 4 includes the construction mechanism and ontology evaluation of the crisp ADD0, which increases the AD knowledge resources' satisfaction. Section 5 introduces the ADD0 fuzzy extension. Section 6 demonstrates the fuzzy ADD0 experiment and results. Finally, the conclusion and future work are presented in Section 7.

II. RELATED WORK

For generating accurate and acceptable CDSS, the knowledge base is the essential component that can semantically represent disease and structure knowledge. Handling this challenge requires three main issues. First, provide semantic

consistency issues that require a detailed analysis of patients. Second, build a complete clinical knowledge base model in the lack of a comprehensive clinical approach. Third, support the integration with the EHR system, which allows for effective management in real-time.

Before developing ADD0, we surveyed the ontology repositories such as BioPortal [19] and recent researches for available ontologies related to AD. There are several existing ontologies of AD with different end goals categorized as storing and recovering AD information, supporting standardization, and suggesting the diagnosis of AD. Regarding to AD knowledge modeling, Semantic Web in Neuromedicine (SWAN) was developed by Ciccarese *et al.* [20] as a standard project related to significant practical research in AD. It focused on storing existing AD knowledge allowing for building publications, digital reference repository, and the semantic web. However, SWAN is not available on any online ontology repositories. For supporting AD research purposes, National Institute on Aging (NIA) published CADRO [21] ontology based on three categories. The first category is the molecular and physiological processes. The second category is the assessment, disease monitoring, and diagnosis. The last category is research and clinical interventions. However, CADRO was not operated in the real-world. For the purpose of supporting SemBiP semantic portal, it is a digital library specialized in reviewing AD scientific papers, Dramé *et al.* [22] built the OntoAD ontology based on reusing the available terminological resources. It is a bilingual (English-French) ontology for modeling AD knowledge. However, OntoAD has not been validated by using a real application. Henry *et al.* [23] tried to interest the pathophysiology of AD that can improve understanding of the AD

and generate new hypotheses. They converted AlzPathway, a disease map that detailed AD pathophysiology, into a consistent ADMO ontology.

Jensen *et al.* [24] developed Neurological Disease (ND) Ontology-based on BFO. It specialized in representing the key aspects of neurodegenerative diseases, including symptoms, signs, diagnosis, interventions, and evaluations in the context of clinical practice. Later, Cox *et al.* [25] extended ND ontology and developed NeuroPsychological Testing Ontology (NPT) that includes new classes and annotation of a large group of neuropsychological tests. They provided more representation of the cognitive functions, but NPT suffered from complexity. Since it had more classes out the field in which this ontology is focused. Batrancourt *et al.* [26] used DOLCE as the primary basis and developed OntoNeuroLOG ontology aimed to spot on the brain and its cognitive functions. It is considered one of the complete ontologies. However, its biggest disadvantage could be a bad impact on reasoning time.

Regarding ontologies as diagnosis support, it is used to aid physicians in the early disease diagnosis. It often includes facts or given axioms, ontology with semantic reasoner to infer possible diagnosis. One of the important knowledge in these ontologies related to the tests carried out to patients as the neurological, neuropsychological, radiological, genetic, and metabolomic tests.

Malhotra *et al.* [27] tried to cover the different aspects of the AD, including non-clinical, clinical, risk factors, diagnosis, and treatments and developed Alzheimer's Disease Ontology (ADO) based on BFO. ADO is a semantic, standardized, biological representation, and allowing retrieval and inference of the information. However, ADO has low utilization of existing ontologies and gained more attention to disease mechanisms. Sanchez *et al.* [28] extended MIND based on SNOMEDCT and SWAN ontologies to support AD research. For the detection of AD, MIND used semantic reasoning over 350 patients. It was challenging to be reused because it had a brief description. Besides, it was only limited to the diagnosis concept and ignored the different cognitive processes. Zhang *et al.* [29] proposed ontology-driven decision support for MCI diagnosis by detection of the thickness of the cortical cortex through magnetic. However, This ontology ignored necessary tests, such as neuropsychological tests, and Just focus on an MRI imaging approach.

Zekri *et al.* [30] proposed AlzFuzzyOnto as fuzzy AD diagnosis ontology. It used MIND as a basic ontology and tried to overcome imprecision and uncertainty in some significant terms and ontology concepts using the fuzzy logic. AlzFuzzyOnto was developed using classes, which are tests, tests value, patient, doctor, diagnosis, enrollment, and follow-up. However, the validation of this ontology had not been carried out. To facilitate remote monitoring of cognitive impairment patients, Ivascu *et al.* [31] developed a multiagent ontology. This system requires automated devices/sensors and data privacy improvements.

According to the real-world scenario and ability to reuse, ADO and ADMO are the available ontologies developed according to BFO. ADMO spotlight the biological description by representing the complexity of AD pathophysiology. ADO cared more about the disease mechanism and ignored patient data. Finally, ADO is the most suitable ontology to be reused in developing our ontology ADDO. It contains classes like gene, brain region, diagnosis procedure classes that might be useful for importing into ADDO.

AD is a dangerous disease that causes death to a large proportion of the elderly in the US, as it is ranked third after heart disease and cancer [32]. Concerning the current AD ontology, there are limited studies that have been presented toward semantically intelligent knowledge. They do not commensurate with the severity of this disease. Most of these ontologies terms, relations, and axioms are not clear, and many of them are not publicly available, such as CADRO, MIND, and AlzFuzzyOnto [33]. Other studies ignored the analysis of patients' characteristics like ADO. None of them provide complete clinical knowledge of AD. Most of them are crisp ontology that cannot deal effectively with uncertainty and relationships in real-medical knowledge. Their support for integration with the EHR system was weak. To avoid the aforementioned limitations, we proposed ADDO ontology to be a good core of our CDSS for AD diagnosis. Its a standard, comprehensive, effective in dealing with real-medical knowledge. It provides a complete clinical knowledge of AD. Besides, it supports interoperability with heterogeneous data.

III. THE PROPOSED FUZZY ONTOLOGY-BASED CDSS MODEL

In this study, an ontology-based fuzzy CDSS is presented to warn patients who are at high risk of having AD. It is able to classify NC, MCI, and AD patients based on comprehensive clinical characteristics. Fig. 2 presents the architecture of the established framework. It is divided into three main components. First, the ADDO construction mechanism aims to provide AD-related knowledge using ontological knowledge representation to support physicians' diagnosis decision-making. So, ADDO is the core component of an intelligent CDSS. According to the real-medical scenario, diagnosis tests have different linguistic values that were not possible using the crisp ontologies. Second, the ADDO is fuzzified based on the FuzzyOWL2 plug-in to enhance ADDO ontology for representing uncertain concepts and relationships in real-medical knowledge, thus facilitating decision-making efficiency results. Third, the rule base construction handles the generation of SWRL rules. An accurate rule base improves the accuracy and the interpretability of the CDSS.

Rules are extracted based on learning data mining techniques, such as Bayesian networks, neural networks, and fuzzy decision trees, with the domain expert's guide. A Fuzzy Decision Tree (FDT) is very suitable for the induction of simple medical decisions. It is applied in the medical decision by examining ambiguously and incompletely clinical data. We selected the FDT to keep interpretability, investigate

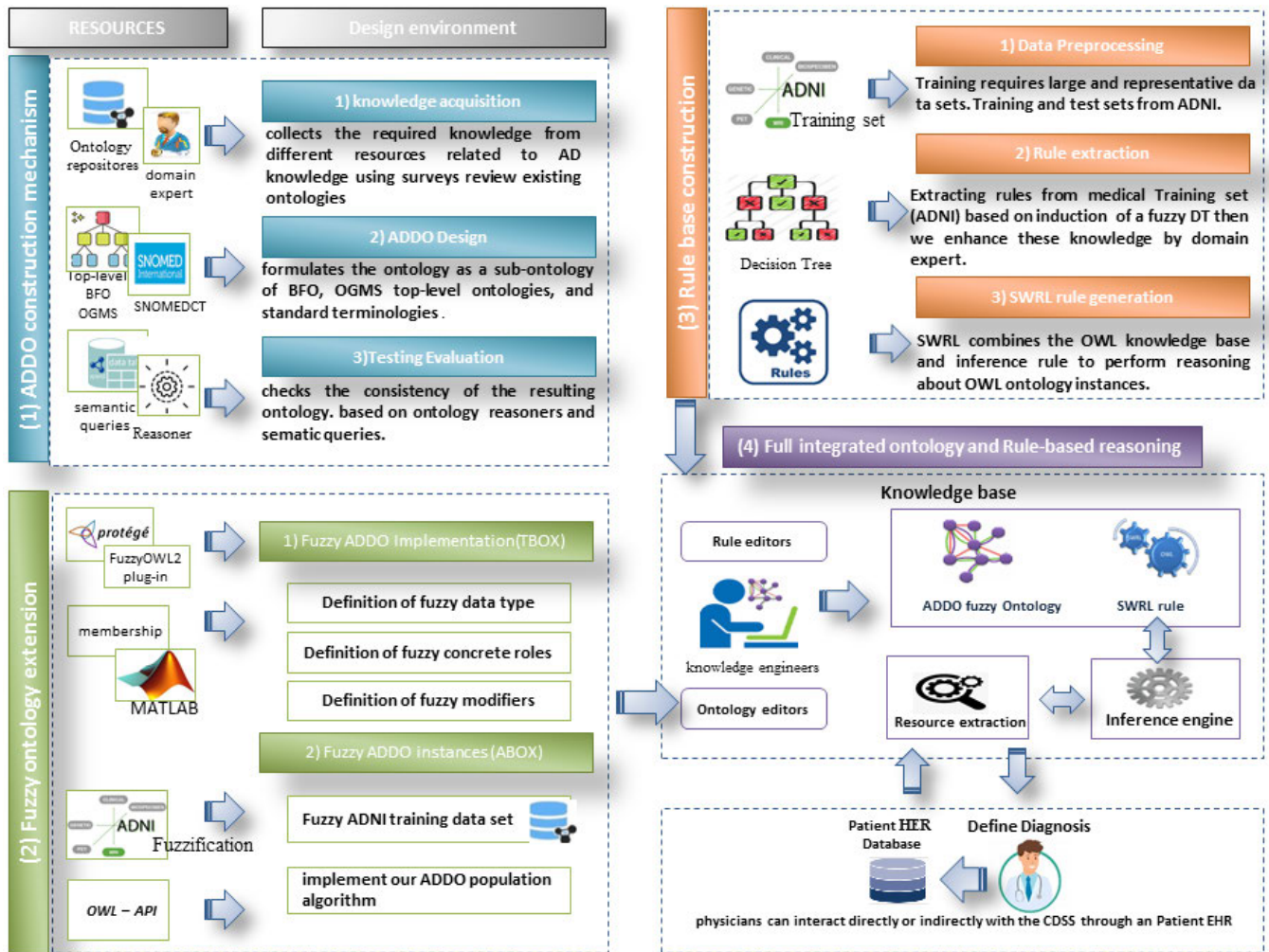


FIGURE 2. The proposed fuzzy ontology-based CDSS model.

medical error, robustness, and applicability of resulting rules. The rule set is trained by ADNI data of NC, MCI, and AD patients inducted by the FDT algorithm.

Full integrated ontology and rule-based reasoning include the following components. First, the database provides semantic interoperability for the mapping of patient’s profile data, demographic data, the longitudinal progression of the patients visit, gene, MRI image features, symptoms, medical history, medical disease history, medication intake, diagnosis examination test including physical examination, chemical biomarker (laboratory results, behavioral, and cognitive tests), and complications. Second, the knowledge base comprises the fuzzy ADDO and rule-based model using SWRL. Third, fuzzification transforms the patient data as test values into degrees of the match with linguistic values in fuzzy ADDO ontology. Fourth, fuzzy inference uses some fuzzy if-then rules to map a given input to an output. Fifth, defuzzification transforms fuzzy results of inference to crisp output values. Sixth, the query engine handles physician’s queries. Seventh, the reasoning engine checks the consistency and deduces diagnosis decisions.

IV. METHODOLOGY FOR ADDO DEVELOPMENT

CDSS is essential to improve healthcare practice and reduce preventable medical errors by offering the right, efficient, and effective decisions at the right time. CDSS, which is provided with consistent ontology and integrated with patient databases, are the main aspects of proactively. The most critical CDSS component is its knowledge base. This knowledge base can be represented and structured using ontologies. In which ontology plays a key role in semantic reasoning and making inferences about diagnoses using the collected patient data. Concerning semantic intelligence, ontologies can add more power to CDSS [34]. For example, to mimic doctors’ reasoning, CDSS cannot avoid semantic relationships between some patient’s features, such as diseases, symptoms, and drugs. CDSS with ontologies can handle this challenge because it can offer several advantages as they can be reused in similar domains, easy maintenance, support knowledge sharing, semantic integration with EHR, and other reasoning techniques. As a CDSS support, ontologies are designed for a practical purpose to be integrated as a submodule working as a knowledge database into a larger system.

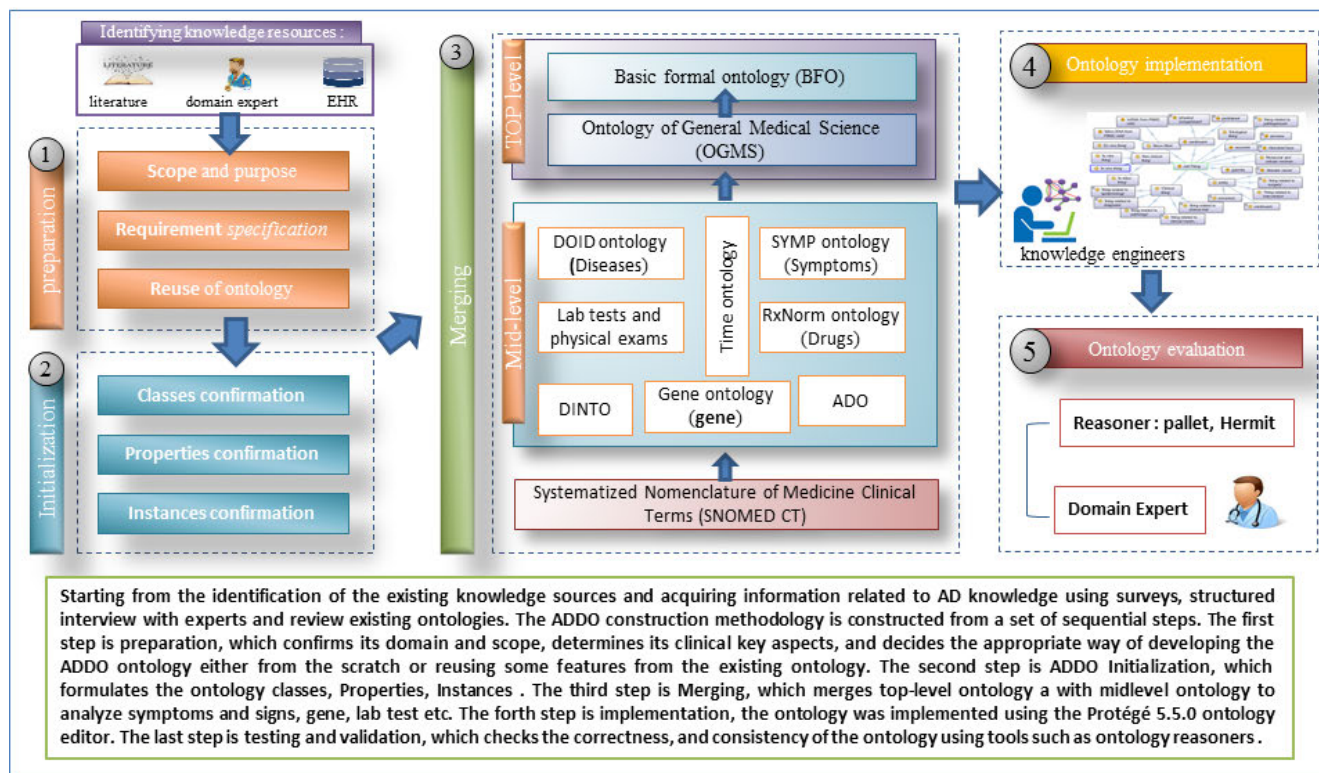


FIGURE 3. The ontology construction based on top-mid level ontology.

Building coherent, interoperable, consistent, and sharable ontology related to AD is a challenge. It requires a comprehensive clinical approach. The patient’s clinical characteristics and data must be presented at the point of care, such as disease, complications, laboratory examination, physical examination, symptoms, medical history, medication, and genetics. It includes the ability to design strategies to diagnose AD, detect risk levels (NC, MCI, and AD), and monitor their severity according to the complete medical profile.

This section discusses the construction of ADDO ontology for AD diagnosis. Hopefully, ADDO introduces interesting features for classifying NC, MCI, and AD patients and will play a significant role in developing a standard, intelligent, and interoperable CDSS. We have imported top-level ontology via BFO and OGMS with the proposed ADDO to reduce the possibility of errors and support semantic interoperability between ADDO and other systems. Besides, preserve the reusability, consistency, and formality of the resulting knowledge. ADDO construction has five phases, including the preparation as a first and fundamental stage for acquiring information related to AD knowledge and determining its clinical aspects, and decides the appropriate way of developing the ADDO ontology. The second phase is ADDO initialization, where features are collected, and a description is provided about ontology classes, properties, and instances. In the third phase, BFO and OGMS merged into ADDO as the top-layer ontology. It provides a general top level

structure that can support interoperability between existing systems and ADDO. Finally, implementation and evaluation of ADDO check the correctness and consistency. Fig. 3 illustrates the ADDO construction framework.

A. ADDO PREPARATION

1) SCOPE AND PURPOSE DETERMINATION

One of the first and essential steps in ontology construction is defined by its domain and scope. It is a significant step to ensure the validation of the specific domain before building an ontology. In this paper, our purpose is to develop a standard disease diagnosis of a coherent ontology associated with Alzheimer’s patients that includes comprehensive information from different sources to improve reasoning accuracy. The physician or medical students are the intended users of the ADDO. ADDO makes decisions in the following manner. First, the ADDO receives the account of patient profile data, including diseases, diagnostic tests, family history, symptoms, medications, patient history, and physical examination. Then, the reasoner performs reasoning on ADDO’s knowledge base, and the inferred diagnosis decision is added to the knowledge base.

2) REQUIREMENT SPECIFICATION

As mentioned, it is essential to identify some essential information to build this ontology. There are many medical key

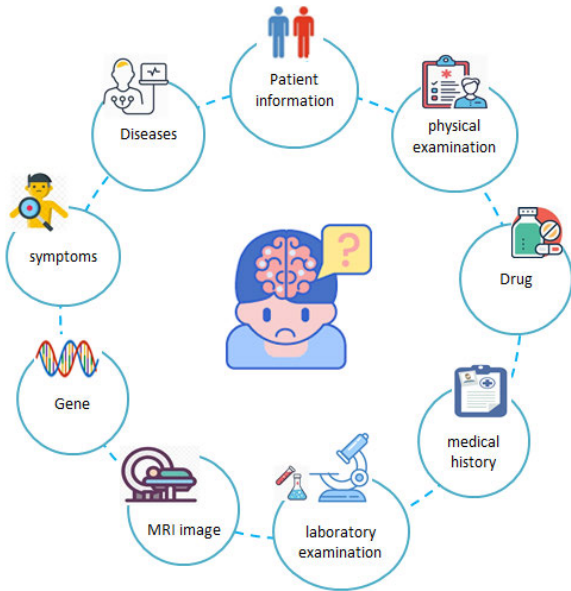


FIGURE 4. The medical key aspects covered by ADDO.

aspects related to AD that must cover, as shown in Fig. 4. ADDO represents the significant aspects of patient characteristics under the patient profile and his periodic visits data in a standard way. Each patient profile has patient characteristics and diagnosis. ADDO ontology provides a possible diagnosis for the patient subject to the responsibilities outlined in its chronic diseases and drugs.

$$patient\ profile\ structure = \{C, D(C)\}. \quad (1)$$

where C is the patient characteristics, including:

- 1) Demographic data: participant ID, age at baseline, birth date, gender, participant education (years), marital status, ethnic category, and racial categories.
- 2) Vital sign: blood pressure value, height, respiration, temperature value, weight, and seated pulse rate.
- 3) Symptoms: early symptom of AD, symptom of MILD AD, symptom of moderate AD, and symptom of severe AD).
- 4) Pain: abdominal pain, acute pain, chest pain, headache, and earache.
- 5) Medical history: smoking history value, alcohol intake value, drug abuse, major surgical procedures, and allergies or drug sensitivities.
- 6) Family history: monitoring of patient relatives who have a family history of AD or dementia.
- 7) Patient Visit: longitudinal progression of the participant visit, such as visit code and visit date.
- 8) Complications: the likelihood of suffering from other complications, such as acute disease or chronic disease related to cancer, liver, diabetes, hepatic, cardiovascular, and kidney.
- 9) Medication: define drugs used in treatment as Donepezil and Axura.

TABLE 1. The diagnostic test categories.

Tests categories	features
Brain Imaging	Positron emission tomography (amyloid_beta_deposition, FDG, glucose_utilization, PiB_PET, etc.) Magnetic resonance imaging (functional MRI(fcMRI, MRS))
Brief Screening Test	Montreal_Cognitive_Assessment, AD8, Clock_draw_test, Mini_cog, Mini_mental_state_exam, etc.
Cerebrospinal fluid test	Abeta_140_test, Abeta_142_test, Amyloid_beta_42_peptide_and_tau_protein_correlation, neurofilament_test, Tau_test, etc.
Cognitive Test	Alzheimer_s_Disease_Assessment_Scale, Blessed_Information_memory_concentration_test, cognitive_reserve_questionnaire, Memory_orientation_screening_test, Mini_mental_status_examination, etc.
Mood Evaluation	Apathy_evaluation, Assesment_of_Anxiety_or_Depression
Neuropsychological test	Neurobehavioral_cognitive_status_examination, Neuropsychiatric_inventory, Alzheimer_s_disease_assesment_scale_cognitive, Simple Word Test, etc.
Blood test	Angiography, kidney_function_screening, HIV_testing, PSEN1_test, PSEN2_test, Red_blood_cell_count, Serum_Glutamic_pyruvic_tranaminase_testing, Thyroid_Functioning, Toxic_screening, Vitamin_B12_test, White_blood_cell_count, etc.
Physical state Examination	Blood_Pressure_checkup, Enquiry_about_Diet_and_Nutrition, Enquiry_about_Usage_of_Tabacco_and_Alcohol, Hearing_test, Lung_Checkup, Pulse_rate_checkup, Vision_test, etc.
Genes test	ApoE_genotype_test

- 10) Diagnostic tests: They categories results. The diagnostic tests are described by a huge number of features. Some of this feature is shown in Table 1.

$$D(C) = \{NC, MCI, AD\}. \quad (2)$$

where $D(C) = AD$ diagnosis. The patient is described by these features, and the ADDO suggests a diagnosis of patient conditions.

3) REUSE OF ONTOLOGY

To build a standard and coherent ontology, we may exclude the model’s development from scratch and support the adoption of some features from the existing ontology. It avoids some problems, including inconsistencies and redundancy problems in the class hierarchy, unstable references, and conflict in the term names. Most of the current ontology construction methodology comprises many terminologies (as SNOMED CT and RxNorm) and standard ontologies (like SYMP and DOID). It increases the quality of patient care by supporting the enrichment of the ontology, improving data analysis, and providing consistent representation.

This step produces a mid-level ontology to analyze symptoms, drugs, disease, and other AD concepts. We build symptom classes based on Symptom Ontology (SYMP) [35]. Time classes are based on TIME ontology [36]. Disease classes are

TABLE 2. Description of some ADDO classes.

Class Name	Description		
	Description	Subclasses Example	Class hierarchy
Patient	Person with memory problems, some of them may have SCI or MCI but others suffer from AD.		⊆ BFO_0000023
demo graphic	Include factor as gender, age, and race	Age, gender, Education years, Marital Status	⊆ BFO_0000023
Relative	A member of the patient’s family is also infected	Brother, father, mother, sister	⊆ BFO_0000023
Patient Profile	facilitate the monitoring of patient characteristics of diagnosis, complications, lab tests,etc		⊆ BFO_0000019
Patient Visit	Indicate the longitudinal progression of the participant visit		⊆ OGMS_0000096
AD disorder	physical basis of disease	sleep_disorder, neuronal_damage	⊆ OGMS_0000045
disease	Something wrong exists due to one or more disorders in the organism	neurodegenerative, tauopathy, AD	⊆ BFO_0000016
Adverse Effect	a response to a drug	brain, hair, skin, behavior and neurological AE	⊆ BFO_0000016
Vital sign	Vital signs as, Weight, Height	Heartbeat, blood pressure, Weight, Temperature,	⊆ BFO_0000016
patient history disease	Diseases suffered by the patient	Acute disease, chronic disease	⊆ OGMS_0000029
symptom	patient symptoms that define its Persistent physical disturbance	Dizziness, Chest pain, Headache	⊆ SYMP_0000410
Blood test	Collecting observation about quality of patient-derived specimen	Thyroid_Functioning, Vitamin_B12_test, Red_blood_cell_count	⊆ OGMS_0000056
Diagnostic test	Tools for Alzheimer diagnosing as Cognitive Test, Mood Evaluation, Cognitive Test	Neuropsychological test,Brain Imaging, Mood Evaluation, Cognitive Test, Simple Word Test	⊆ OGMS_0000104
Physical examination	check the symptoms of AD by examining the body physical signs	Head, Eyes, Ears, Nose and Throat, Neck, Skin	⊆ OGMS_0000057
Medications	Define drugs to treat Alzheimer	Acetophenazine, amitriptyline, vitamin E.	⊆ BFO_0000040
Gene	DNA structure played a role in keeping the body’s cells healthy	APOE, A2M, APP	⊆ BFO_0000040
Brain region	Define component of the brain	Cerebellum, cortex, Hippocampus, basal ganglia region.	⊆ BFO_0000006
functional MRI	check the living brain and Locate the areas of the brain that are affected.	Magnetic resonance spectroscopy, MRI.	⊆ OGMS_0000104
Diagnosis	Determining the AD severity by examining the nature and circumstances of the patients	Diagnosis of mild co mild cognitive impairment	⊆ OGMS_0000073

based on Human Disease Ontology (DOID) [37]. Adverse effect import from The Drug-Drug Interactions Ontology (DINTO) [38]. The adverse effect can be added to related patient history drugs, complications, and drugs. Drugs classes are based on RxNORM Ontology [39] to collect the most suitable drugs, contraindications, dosages, and other critical features. Finally, the gene classes, brain region, and diagnostic procedures are extracted from ADO [40]. Then connect the mid-level ontology with a top-level ontology to provide integration of medical information and ADDO.

B. INITIALIZATION

1) CLASSES’ CONFIRMATION

To build a custom disease diagnosis ontology, the first step involves checking and collecting many medical conditions and features to make the decisions as complete as possible. These features were collected from medical experts, recent

literature, and electronic medical record. For example, MCI patients have some symptoms, such as dizziness, memory problem, judgment of the time, accomplishment planning steps, or visual perception problems. It is essential to understand the nature and types of medications, as appropriate medication intake can reduce AD patients’ complications. Maintain a timeline of patient visits and determine their severity as NC, MCI, or AD. Hence, classes as patients, relative medications, vital signs, lab tests, and medical history are utilized for ADDO to develop better diagnosis decisions for AD, as shown in Table 2. The illustration of ADDO architecture is shown in Fig. 5.

2) ADDO PROPERTIES

To represent domain knowledge, relying solely on the class hierarchy is not sufficient. It should also focus on the internal structure of these classes that represent relations. In the

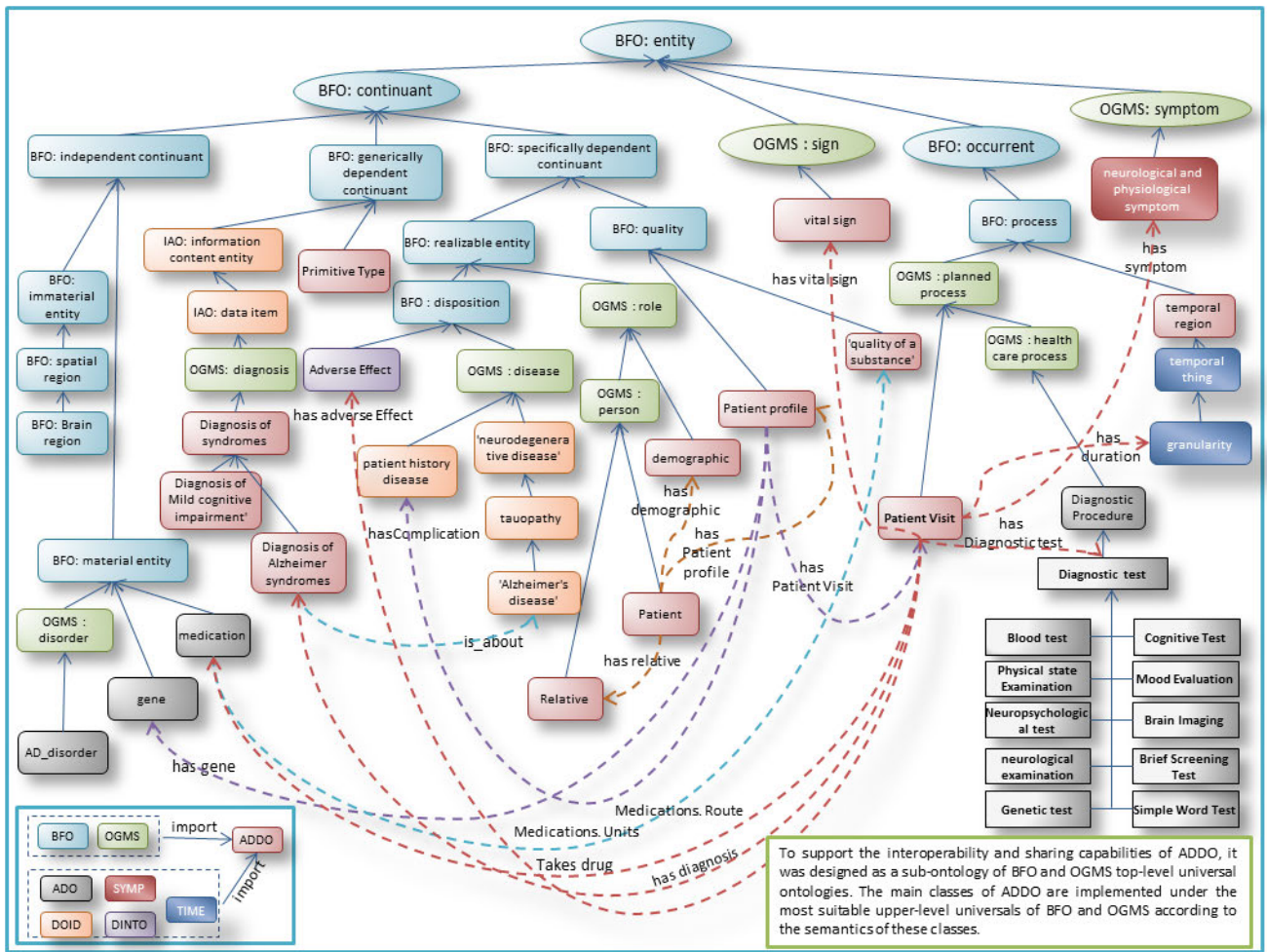


FIGURE 5. The graphical overview of foundational entities of ADDO.

ontology domain, relations are represented by properties. They are divided into object and data properties. Object properties specify objects and define how links and associations are formed between ontology concepts. For example, the patients' visit can define the object property, has_Visit, which can be defined by $P \text{ has_visit } V = \text{def}$. For every PatientProfile individuals p of P , there are some individuals Visit v of V such that $p \text{ has_Visit } v$. Data properties connect individuals with literals, which are used to define the ontology concepts' values. For example, the Thyroid Stim Hormone (Test AXT117) for a specific patient is 6.26, and we may apply the data properties (has_value) to has_value (AXT117, 6.26). For further clarification, Table 3 provides ADDO object properties. The list of data properties of ADDO is shown in Table 4.

3) ADDO AXIOMS

To achieve precise semantics, we infer additional knowledge and support the computational search in ADDO. It is managed by a group of axioms that formulate the logical definitions of its classes and properties. Some of these axioms are explained as follow:

The Person class and its subclasses Patient and Relative are defined as:

$$\text{Person} \equiv (\text{Patient} \sqcup \text{Relative})$$

$$\text{Person} \sqsubseteq \text{role} \sqcap (\forall \text{ has_demographic. demographic})$$

$$\text{Patient} \sqsubseteq \text{Person}$$

$$\sqcap (\forall \text{ has_patientProfile. patientProfile})$$

$$\sqcap (\exists \text{ has_Contact. Relative})$$

$$\text{Relative} \sqsubseteq \text{Person}$$

$$\sqcap (\exists \text{ Relative. hasDementia. boolean})$$

$$\sqcap (\exists \text{ Relative. hasAD. boolean})$$

$$\sqcap (\exists \text{ Relative. Subject. Patient})$$

The demographic class is used to collect the subjective data, such as participant ID, age, education in years. This class is implemented as follows:

$$\text{demographic} \equiv (\text{PTID} \sqcup \text{age} \sqcup \text{birth date} \sqcup \text{gender} \sqcup \text{education} \sqcup \text{ethnic} \sqcup \text{marry} \sqcup \text{racial} \sqcup \text{contact})$$

$$\text{demographic} \sqsubseteq \text{role}$$

$$\sqcap (\forall \text{ demographic. value. primitiveType})$$

Each patient has one patient profile. It is used to model all patient characteristics including familyHistory,

TABLE 3. Description of some ADDO object properties.

Object properties	Description	
	Domain	Range
has_patientProfile	Patient	Patient_profile
has_demographic	Person	demographic
demographic.value	demographic	primitiveType
has_FamilyHistory	patient profile	Relative
Relative.hasDementia	Relative	boolean
Relative.hasAD	Relative	boolean
has_medicalHistory	patient profile	medicalHistory
medicalHistory.value	medicalHistory	boolean
has_gene	patient profile	gene
gene.Value	gene	integer
hasComplication	patient profile	patient history disease
patientHistoryDisease.value	patient history disease	severityCode
has_visit	patient profile	Patient Visit
Visit.Code	PatientVisit	visit_code
Visit.Date	PatientVisit	date
has_disposition	PatientVisit	disease
DiseaseContradictWithDrug	disease	medication
has_symptom	PatientVisit	symptom
SYMP.CEASE	symptom	date
SYMP.CHRON	symptom	ChronicityType
SYMP.CONTD	symptom	boolean
SYMP.ONSET	symptom	date
SYMP.SEVER	symptom	severityCode
has_diagnosis	PatientVisit	diagnosis
Diagnosis.severity	Diagnosis of disease	severityCode
Diagnosis.value	Diagnosis of disease	risk_level
has_Diagnostic_test	PatientVisit	Diagnostic test
Diagnostic_Procedure.Date	Diagnostic Procedure	date
Diagnostic_Procedure.Value	Diagnostic Procedure	decimal
has_CognitiveTest	PatientVisit	Cognitive Test
has_laboratoryTest	PatientVisit	laboratory test
has_MRI	PatientVisit	Magnetic resonance imaging
MRI.features	Magnetic resonance imaging	Brain region
MRI.values	Brain region	integer
has_vital	PatientVisit	Vital sign
Vital.value	Vital sign	decimal
Vital.unit	Vital sign	code
is_about	AD diagnosis	Alzheimer's disease
has_disease_severity	diagnosis	Severity
has_duration	patient	PatientVisit
takes_drug	PatientVisit	Medication
Medications.Adverse_Event	medication	adverseEvent
Medications.continuing	medication	boolean
Medications.Date_Ended	medication	date
Medications.DateBegan	medication	date
Medications.Dose	medication	integer
Medications.drugContradictDithDisease	medication	disease
Medications.drugContradictWithDrug	medication	medication
Medications.Route	medication	route of administration
Medications.Units	medication	dose form

medicalHistory (related to allergies, drug sensitivities, smoking, alcohol intake, and previous surgical), gene, complication, and at least one patient visit. This class is designated as follows:

TABLE 4. The description of some ADDO data properties.

Data properties	Description	
	Domain	Range
has_boolean_value	primitiveType	boolean
has_value	primitiveType	int , float
has_maximum_dose	primitiveType	float
has_risk	primitiveType	risk_level
has_severity	primitiveType	severityCode

patientProfile \sqsubseteq quality
 \sqcap (\exists has_FamilyHistory.Relative)
 \sqcap (\exists has_medicalHistory.medicalHistory)
 \sqcap (\forall has_gene.Gene)
 \sqcap (\exists has_Complication.patient historydisease)
 \sqcap (≥ 1 has_visit.PatientVisit)
 \sqcap (\forall Profile.Subject.Patient)

The diseases that the patient suffers from are modeled by the patient history disease class as follows:

patient history disease \sqsubseteq disease
 \sqcap (=1 has_disease_duration.Time interval)
 \sqcap (≥ 1 has_severity.severityCode)
 \sqcap (\exists DiseaseRecommendedDrug.Medication)

PatientVisit is one of the main classes of ADDO where all longitudinal progression of the patient visit characteristics are collected. This class including visit data (i.e., visit code, examination date) diagnostic test (i.e., cerebrospinal fluid test, cognitive test, laboratory test), complications (i.e., disease), symptoms, adverseEvent (i.e., taking an wrong drug), diagnosis, etc.

PatientVisit \sqsubseteq health care process
 \sqcap (\forall Visit.Code.visit_code)
 \sqcap (\forall Visit.Date.date)
 \sqcap (\forall Visit.Time.timing)
 \sqcap (\exists has_disposition.Disease)
 \sqcap (\exists has_AdverseEvent.adverseEvent)
 \sqcap (\exists has_symptom.Symptom)
 \sqcap (≥ 1 has_diagnosis.Diagnosis)
 \sqcap (≥ 1 has_diagnosis_severity.severityCode)
 \sqcap (\forall has_Diagnostic_test.DiagnosticTest)
 \sqcap (\exists has_Complication.patient historydisease)
 \sqcap (\exists takes_drug.Medication)
 \sqcap (\exists has_vital.VitalSign)
 \sqcap (\exists has_Pain.Pain)
 \sqcap (\exists has_physicalExamination.physical Examination)
 \sqcap (\forall Visit.context.patientProfile)

One of the critical classes for ADDO is the disease class whose characteristics specifies (i.e., code, contradicted drugs, and recommended drug). This class is implemented as follows:

Disease \sqsubseteq disposition
 \sqcap (\exists DiseaseContradictWithDrug.Medication)
 \sqcap (\exists DiseaseRecommendedDrug.Medication)

$\sqcap (\exists \text{has_code.code})$
 $\sqcap (\forall \text{Disease.context.patientProfile})$

The neurological and physiological symptom class is used to model patient's symptom (i.e. onset data, chronicity, severity, and continue). We imported the possible AD symptoms from SYMP ontology and implemented it as follows:

neurological and physiological symptom \sqsubseteq symptom
 $\sqcap (\exists \text{SYMP.CEASE.date})$
 $\sqcap (\exists \text{SYMP.CHRON.ChronicityType})$
 $\sqcap (\exists \text{SYMP.CONTD.boolean})$
 $\sqcap (\exists \text{SYMP.ONSET.date})$
 $\sqcap (\exists \text{SYMP.SEVER.severityCode})$
 $\sqcap (\forall \text{SYMP.context.patientProfile})$

For drugs used in AD treatment, we tried to implement all of the properties that can define the medication class as follows:

medication \sqsubseteq material entity
 $\sqcap (\exists \text{Medications.Adverse_Event.adverseEvent})$
 $\sqcap (\exists \text{Medications.continuing.boolean})$
 $\sqcap (\exists \text{Medications.Date_Ended.date})$
 $\sqcap (\exists \text{Medications.DateBegan.date})$
 $\sqcap (\exists \text{Medications.Dose.integer})$
 $\sqcap (\exists \text{Medications.Dose.integer})$
 $\sqcap (\exists \text{Medications.drugContradictDithDisease.disease})$
 $\sqcap (\exists \text{Medications.drugContradictWithDrug.medication})$
 $\sqcap (\exists \text{Medications.Route.routeofadministration})$
 $\sqcap (\exists \text{Medications.Medications.Units.doseform})$
 $\sqcap (\forall \text{Medications.context.patientProfile})$

AD diagnosis requires huge number of diagnostic tests categories (i.e., brain imaging, neuropsychological, cognitive, and lab tests). We imported the possible AD diagnostic test classes from ADO ontology and implemented it as follows:

DiagnosticTest $\equiv (\text{Brain Imaging} \sqcup \text{Genetic_test} \sqcup \text{Cerebospinal fluid test} \sqcup \text{Neuropsychological test} \sqcup \text{Cognitive Test} \sqcup \text{Mood Evaluation} \sqcup \text{laboratory test})$
 DiagnosticTest \sqsubseteq diagnostic process
 $\sqcap (\exists \text{Diagnostic_Test.Date.date})$
 $\sqcap (\exists \text{Diagnostic_Test.Value.decimal})$
 $\sqcap (\forall \text{Diagnostic_Test.context.patientProfile})$

4) ADDO INSTANCES

An ontology represents data in the form of triples (subject-predicate-object) and is connected in the form of a directed labeled graph (link-by-link). Mapping data to ontology (e.g., RDF, OWL) has several advantages [41], such as data becomes self-describing when semantics are added, facilitate data integration, and support data source discovery and sharing. ADDO is a general ontology and can be applied with any data sources related to AD diagnosis. This paper used data as a case study that originated from the ADNI (adni.loni.usc.edu). It was initiated in 2003 to pose challenges

to increasing public awareness of AD and other dementias. It provides a multi-categorical data nature, including MRI image data, PET image data, biospecimen data, clinical data, and genetics data. ADNI data are made available in spreadsheets (CSV).

In this work, we employed Cellfile [42], which is the Protégé-based plugin to perform a comprehensive mapping of the ADNI spreadsheet content to OWL entities and axioms. Cellfile provides an automated process to generate the mapping process. It converts every CSV table into a class and each table column into a data property. This approach did not yield satisfactory results. It increases the number of data properties and decreases the number of object properties. It makes ontology shallowness and related only to ADNI structure.

For example, ADNI contains an ADSXLIST.csv file that describes the patient symptoms checklist. It contains many features like RID (Participant roster ID), VISCODE, USER-DATE, EXAMDATE, and 28 symptoms only related to AD as AXNAUSEA(Nausea), AXVOMIT(Vomiting), AXDIARRH(Diarrhea), etc. Each symptom feature has an Absent or Present value. For mapping this table in a traditional way using Cellfile. We have patient symptoms restricted with 28 data properties only. That is further from reality. Since the patient symptoms should be more comprehensive and not defined by a limited number of data properties, there are certainly cases of patients who may suffer from other symptoms.

To avoid the previous problem, ADDO has comprehensively built that supports interoperability in the following manner. First, we import symptom classes from standard SYMP ontology and place them according to BFO and OGMS principles. Then, we add an object property called has_symptom (Domain "PatientVisit", Range "symptom"). For every PatientVisit individuals v of V , there are some individuals symptom s of S such that v has_symptom s . Then, we add many object properties (Domain "Symptom", Range "primitive Type") to describe symptom data as SYMP.CEASE (Cease Date), SYMP.CHRON (Chronicity), SYMP.CONTD (Is the event ongoing?), SYMP.ONSET (Onset Date), SYMP.SEVER (Severity). The primitive type has data property as hasValue, has_severit, where is the patient symptom value added (connect individuals with literals). So, data are mapped into more closely mimic reality categories. It makes the mapping of ADNI or other related data to OWL classes more straightforward and yields better results.

C. MERGING TOP-LEVEL ONTOLOGY

To create a complete class hierarchy of ADDO, some classes are built from scratch, such as patient, patient profile, and patient visits. Other classes are imported from standard ontologies, such as DOID and SYMP. ADDO is fully developed as an extension of BFO and OGMS. They are ontological structures to support semantic interoperability by offering reuse top-level ontology terms between a significant number

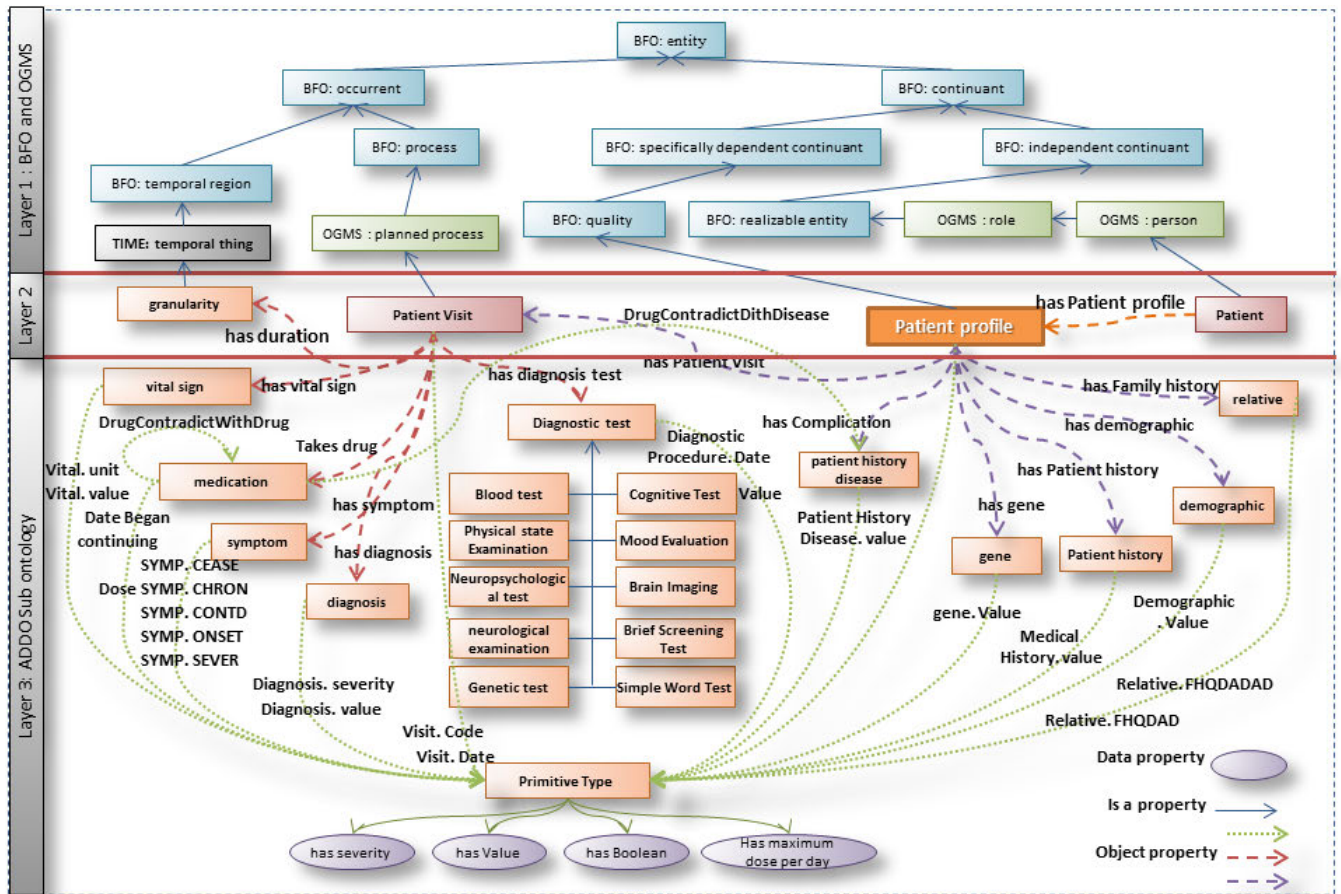


FIGURE 6. The overview of high-level terms in ADDO.

of domain-specific ontologies. OGMS is responsible for utilizing entities in a clinical domain. It recognizes the disease of healthcare. It contains diagnostic procedures, which consist of diseases and their causes and symptoms. It provides high-level terms as ‘disease’, ‘disease course’, ‘diagnosis’, and ‘disorder’.

ADDO classes architecture follows the top-down approach and the *is_a* hierarchy, which is the backbone of every ontology. These classes were added under the most relevant concepts of BFO and OGMS. For example, the ADDO’s ‘disease’ class is added as a subclass of BFO’s disposition, and the ADDO’s ‘neurological and physiological symptom’ class is implemented as a subclass of OGMS’s symptom.

As shown in Fig. 6, ADDO is constructed by merging three levels of abstraction. The first level is the upper level that uses global ontologies as BFO and OGMS to create a standard ontology. The second level is the mid-level that contains the patient profile, patient visit, and time trying to build the AD diagnosis according to the specific patient profile. The third level is the ADDO subclasses, which are detailed parts for each of the presented mid-level.

D. ADDO IMPLEMENTATION

The ADDO implementation is done by using ontology editors. We used Protégé 5.5.0 editor to develop ADDO. OWL 2

TABLE 5. The ADDO ontology metrics.

Metric	Value
Class count	7060
Subclass axiom count	7338
Axioms count	46274
Object property count	99
Data property count	26
Annotation assertion axiom count	30708
Logical axiom count	7809

language is utilized to express it. ADDO reuses other standard ontologies by importing the needed classes by using OntoFox [43]. It is a web-based ontology tool that supports ontology reuse by fetching ontology axioms and terms. ADNI data is uploaded to ADDO using the Cellfie plugin. Table 5 shows the metric data collected from Protégé.

E. ADDO EVALUATION

It is significant to ensure the correctness and quality of the ontology. We used Hermit (version 1.4.3.456) reasoner and SPARQL semantic queries in Protégé to check the consistency of ADDO ontology. The retrieving information process from ADDO is shown in Fig. 7.

SPARQL is a particularly powerful language used to query data corresponding to the RDF data model. A query about

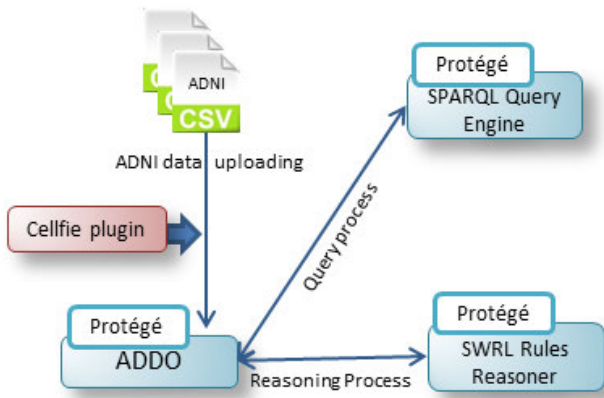


FIGURE 7. The retrieving information process from ADDO.

retrieving information from ADDO is carried out in the following manner. First, ADNI data, which are stored in CSV files, will be uploaded to ADDO using the Cellfie plugin. Second, the SPARQL query engine can access the knowledge base to retrieve information about the patient’s profile. The ontology engineering is not able to express all relations. Ontology can be extended by adding SWRL rules. Moreover, using the SWRL rule reasoner provides the opportunity to infer new facts that can be added to the knowledge base. The next section is showing some questions and their corresponding SPARQL queries.

Q1: Are there any patients with ages 50 to less than 70 years at their baseline visit, with mild to moderate AD, without the APOE4 allele as these would be good candidates for the clinical trial?

```
SELECT DISTINCT ?RID WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_age ?hage;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:has_Visit ?hvisit.
?hvisit ADDO:Visit.Code ?hVcode;
ADDO:has_diagnosis ?hdia;
ADDO:has_Diagnostic_test ?hvlab.
?hvlab ADDO:Diagnostic_test.value ?hvValue;
rdf:type ?vtype.
?vtype rdfs:label "ApoE_genotype_test"^^xsd:string.
?hvValue ADDO:hasValue ?gene.
?hdia ADDO:Diagnosis.value ?hdiav;
ADDO:Diagnosis.severity ?hdias.
?hRID ADDO:hasValue ?RID.
?hage ADDO:hasValue ?age.
?hVcode ADDO:hasValue "bl"^^xsd:string.
?hdiav ADDO:hasValue "AD"^^xsd:string.
?hdias ADDO:hasValue ?severity.
filter((?gene=0) && (?age>=50 && ?age<70) && (?severity="mild" || ?severity="moderate"))}
```

ApoE is an important protein implicated in AD. APOE forms are APOE2 APOE3 and APOE4. The APOE4 protein appears to be ‘toxic’. It is expressed generally in most Alzheimer’s patients because carriers of APOE4 are more likely to develop AD [44].

Q2: Do I have suitable MCI patients at their baseline visit where they are females who are aged over 55 years, low ADAS COG scores and have the APOE variant? order by test date, ADAS score?

```
SELECT DISTINCT ?RID ?ADAS ?date WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_age ?hage;
ADDO:has_gender ?hgen;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:has_Visit ?hvisit.
?hvisit ADDO:Visit.Code ?hVcode;
ADDO:has_diagnosis ?hdia;
ADDO:has_CognitiveTest ?hcog.
?hdia ADDO:Diagnosis.value ?hdiav;
ADDO:Diagnostic_Procedure.Date ?hdate.
?hcog ADDO:Diagnostic_Procedure.Value ?dvalue;
rdf:type ?dtype.
?dtype rdfs:label
"Alzheimer_disease_assesment_scale_cognitive"^^xsd:string.
?dvalue ADDO:hasValue ?ADAS.
?hRID ADDO:hasValue ?RID.
?hage ADDO:hasValue ?age.
?hgen ADDO:hasValue "female"^^xsd:string.
?hVcode ADDO:hasValue "bl"^^xsd:string.
?hdiav ADDO:hasValue "MCI"^^xsd:string.
?hdate ADDO:hasValue ?date.
filter((?ADAS <=15) && (?age>=55))}
order by DESC(?date) ASC(?ADAS)
```

ADAS COG helps in evaluating cognition that can assess which stage of AD person is going through. Its score is ranging from 0 to 70. Score 0 is the least impairment, while score 70 is the most impaired [45].

Q3: List all patients with moderate to severe AD including their visit code, visit date, having the symptom of increased sleeping, Seizures, or Difficulty swallowing including a description of these symptoms (Date of Onset, Severity, Chronicity, Is symptom ongoing?, Ceased Date)?

```
SELECT DISTINCT ?RID ?visitCo ?date ?SYMPdate
?SYMPSeverity ?SYMPCHRON ?SYMPCont ?SYMPCease WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:has_Visit ?hvisit.
?hvisit ADDO:Visit.Code ?hVcode;
ADDO:Visit.Date ?hdate;
ADDO:has_symptom ?hsymp;
ADDO:has_diagnosis ?hdia.
?hdia ADDO:Diagnosis.value ?hdiav;
ADDO:Diagnosis.severity ?hdias.
?hsymp ADDO:SYMP.BSXONSET ?sdate;
rdf:type ?synt;
ADDO:SYMP.BSXSEVER ?sser;
ADDO:SYMP.BSXCHRON ?sch;
ADDO:SYMP.BSXCONTD ?scon;
ADDO:SYMP.BSXCEASE ?sce.
?synt rdfs:label ?SYMP.
?hRID ADDO:hasValue ?RID.
?hVcode ADDO:hasValue ?visitCo.
?hdiav ADDO:hasValue "AD"^^xsd:string.
?hdias ADDO:hasValue ?severity.
?hdate ADDO:hasValue ?date.
?sdate ADDO:hasValue ?SYMPdate.
?sser ADDO:hasValue ?SYMPSeverity.
?sch ADDO:hasValue ?SYMPCHRON.
?scon ADDO:hasValue ?SYMPCont.
?scea ADDO:hasValue ?SYMPCease.
filter((?severity="mild" || ?severity="moderate") &&
((?SYMP="Difficulty_swallowing") ||
(?SYMP="Seizures") ||
(?SYMP="Increased_sleeping")))}
```

Q4: What natural product or vitamin can use to treat Alzheimer’s disease?

```
SELECT DISTINCT (STR(?lab) AS ?natural_product) WHERE {
?subject rdf:type owl:Class;
rdfs:label ?subjectlab.
?directSub rdfs:subClassOf ?subject.
filter (regex(?subjectlab, "natural product"))}
```

```

regex(?subjectlab, "vitamin used in treatment") .
OPTIONAL {?directSub rdfs:label ?lab }
}
ORDER BY ?directSub

```

The result of this SPARQL query is there existing natural products like: Curcumin, Gingko_biloba, docosahexaenoic_acid, omega3_fatty_acids, vitamin_E.

Q5: Is Donepezil covered by the drug used in AD treatment and describe its dose form and route?

```

SELECT DISTINCT ?drug ?dose ?route WHERE {
?subject ADDO:Medications.Route ?hrout;
ADDO:Medications.Units ?hdose;
rdf:type ?type.
?type rdfs:label ?drug.
filter(?drug="Donepezil").
?hrout rdf:type ?trout.
?hdose rdf:type ?tdose.
OPTIONAL {?trout rdfs:label ?route}
OPTIONAL {?tdose rdfs:label ?dose}
}

```

Donepezil [46] is a drug used to treat AD that may improve mental function with mild Alzheimer's.

Q6: Try to find the effect of BMI on the risk of progression AD in subjects with MCI depending on gender, age, and chronic diseases as diabetic neuropathy?

```

SELECT DISTINCT ?RID ?age ?gender(xsd:double
(xsd:float(?weight)/((xsd:float(?height)/100)*
(xsd:float(?height)/100)))
AS ?BMI) WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_age ?hage;
ADDO:has_gender ?hggender;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:hasComplication ?hcom;
ADDO:has_Visit ?hvisit.
?hvisit ADDO:Visit.Code ?hVcode;
ADDO:has_vitalSign ?hvital;
ADDO:has_vitalSign ?wvital;
ADDO:has_diagnosis ?hdia.
?hcom ADDO:patientHistoryDisease.value ?comv;
rdf:type ?com.
?com rdfs:label "diabetic neuropathy"^^xsd:string.
?comv ADDO:hasValue "true"^^xsd:boolean.
?hdia ADDO:Diagnosis.value ?hdiav.
?hdiav ADDO:hasValue "MCI"^^xsd:string.
?hVcode ADDO:hasValue "bl"^^xsd:string.
?hvital ADDO:Vital.value ?hValue;
ADDO:Vital.unit ?hunite;
rdf:type ?vtype.
?vtype rdfs:label "height"^^xsd:string.
?wvital ADDO:Vital.value ?wValue;
ADDO:Vital.unit ?wunit;
rdf:type ?wtype.
?wtype rdfs:label "weight"^^xsd:string.
?hRID ADDO:hasValue ?RID.
?hage ADDO:hasValue ?age.
?hggender ADDO:hasValue ?gender.
{
?hunite ADDO:hasValue "centimeters"^^xsd:string.
?wunit ADDO:hasValue "kilograms"^^xsd:string.
?hValue ADDO:hasValue ?height.
?wValue ADDO:hasValue ?weight. }
union{
?hunite ADDO:hasValue "inches"^^xsd:string.
?wunit ADDO:hasValue "pounds"^^xsd:string.
?hValue ADDO:hasValue ?height.
BIND((xsd:float(?height)*2.54) AS ?height).
?wValue ADDO:hasValue ?weight.
BIND((xsd:float(?weight)*0.45359237) AS ?weight).}

```

Body Mass Index (BMI) [47] is an easy tool that requires only height and weight to measure body fat.

BMI can be calculated according to Formula:(Weight (KG)/(Height(m)*Height(m))).

Q7: What are the MRI data results for the patient with RID number 1018? In addition to his diagnosis and severity at every patient visit?

```

SELECT DISTINCT ?visitCo ?age ?risk ?severity ?feature
?MRIFeatureValue WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_age ?hage;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:has_Visit ?hvisit.
?hvisit ADDO:Visit.Code ?hVcode;
ADDO:has_diagnosis ?hdia;
ADDO:has_MRI ?hMRI.
?hMRI ADDO:MRI.features ?fMRI;
rdf:type ?tMRI.
?tMRI rdfs:label ?feature.
?fMRI ADDO:MRI.values ?vMRI.
?hdia ADDO:Diagnosis.value ?hdiav;
ADDO:Diagnosis.severity ?hdias.
?hVcode ADDO:hasValue ?visitCo.
?hRID ADDO:hasValue ?RID.
?hdiav ADDO:hasValue ?risk.
?hdias ADDO:hasValue ?severity.
?hage ADDO:hasValue ?age.
?vMRI ADDO:hasValue ?MRIFeatureValue.
filter((?RID=1018)&&((?feature="WholeBrain")||
(?feature="Hippocampus")||(?feature="Entorhinal")||
(?feature="Ventricles")||(?feature="Fusiform")||
(?feature="MidTemp")||(?feature="ICV"))).}

```

Magnetic resonance imaging (MRI) [48] is an essential component of the diagnosis of AD. MRI uses a magnetic field and radiofrequency pulses to collect data about brain abnormalities and decrease the volume in some areas of the brain, such as the Hippocampus, Entorhinal, Fusiform, MidTemp, Ventricles, and whole-brain volume. For example, the presence of distortions in the Hippocampus means an inability to form and retain new memories. Distortions in the Middle temporal area lead to recognizing known faces, contemplating distance, and accessing word meaning while reading. Problems with facial recognition are a result of fusiform distortions.

Q8: How many patients are contradicted with Axura?

```

SELECT DISTINCT ?RID WHERE {
?p ADDO:has_RID ?hRID;
ADDO:has_patientProfile ?hprof.
?hprof ADDO:has_Visit ?hvisit;
ADDO:hasComplication ?hcom.
?hvisit ADDO:has_Medication ?hmed.
?hRID ADDO:hasValue ?RID.
{?hmed ADDO:Medications.drugContradictWithDrug ?mcontract;
rdf:type ?Mtype.
?Mtype rdfs:label ?Mlabel .
filter regex(?Mlabel, "Axura", "i").
}union
{ ?hcom ADDO:disease.diseaseContradictWithDrug?dcontract;
rdf:type ?dtype.
?dtype rdfs:label ?dlabel .
filter regex(?dlabel, "Axura", "i").}
}

```

Axura [49] drug used in patients with moderate to severe AD. Its active substance contains memantine hydrochloride. Axura should not be used in two cases. In the first case, the patient is allergic, contradict with memantine hydrochloride. In the second case, the patient is tacking drugs contradict with Axura drug.

Q9: Do I have a virtual list of risk of progression AD in subjects with MCI depending on very low vitamin B-12 and Thyroid_Functioning?

```
SELECT DISTINCT ?RID ?Vitamin_B12 ?Thyroid_Functioning
WHERE {
  ?p ADDO:has_RID ?hRID;
  ADDO:has_patientProfile ?hprof.
  ?hprof ADDO:has_visitCode ?hvisit.
  ?hvisit ADDO:has_Visit ?hVcode;
  ADDO:has_diagnosis ?hdia;
  ADDO:has_Diagnostic_test ?hvlab;
  ADDO:has_Diagnostic_test ?hthlab.
  ?hvlab ADDO:Diagnostic_test.value ?hvValue;
  rdf:type ?vtype.
  ?vtype rdfs:label "Vitamin_B12_test"^^xsd:string.
  ?hvValue ADDO:hasValue ?Vitamin_B12.
  filter(?Vitamin_B12<100).
  ?hthlab ADDO:Diagnostic_test.value ?hthValue;
  rdf:type ?thtype.
  ?thtype rdfs:label "Thyroid_Functioning"^^xsd:string.
  ?hthValue ADDO:hasValue ?Thyroid_Functioning.
  ?hdia ADDO:has_diagnosis_value ?hdiav.
  ?hdiav ADDO:hasValue "MCI"^^xsd:string.
  ?hVcode ADDO:hasValue "b1"^^xsd:string.
  ?hRID ADDO:hasValue ?RID.
}
```

A decrease in the level of vitamin B12 to less than 100 is a dangerous indicator. Patients with this level often have neurological symptoms or an overactive thyroid [50].

Q10: What are Neuropsychological tests associated with AD diagnosis?

```
SELECT ?NeuropsychologicalTest WHERE {
  ?NeuroSub rdfs:subClassOf ?Neuro.
  ?Neuro rdfs:label ?NeuroLab.
  filter regex(?NeuroLab, "Neuropsychological test", "i").
  OPTIONAL {?NeuroSub rdfs:label ?NeuropsychologicalTest}}
```

The sparql query gets a list of the Neuropsychological test associated with AD diagnosis.

Q11: List all patients with their diagnoses at baseline visits who have a history of smoking or alcohol Intake and suffering from a specific disease with the disorder of cardiac function or disorder of coronary artery?

```
SELECT DISTINCT ?RID ?risk ?mHistory ?HistoryDisease
WHERE {
  ?p ADDO:has_RID ?hRID;
  ADDO:has_patientProfile ?hprof.
  ?hprof ADDO:has_medicalHistory ?medical;
  ADDO:hasComplication ?hcom;
  ADDO:has_Visit ?hvisit.
  ?hvisit ADDO:Visit.Code ?hVcode;
  ADDO:has_diagnosis ?hdia.
  ?hdia ADDO:Diagnosis.value ?hdiav.
  ?hVcode ADDO:hasValue "b1"^^xsd:string.
  ?medical ADDO:medicalHistory.value ?mv;
  rdf:type ?mHistory.
  ?mv ADDO:hasValue "true"^^xsd:boolean.
  ?hRID ADDO:hasValue ?RID.
  ?hdiav ADDO:hasValue ?risk.
  ?hcom ADDO:patientHistoryDisease.value ?comv;
  rdf:type ?ctype.
  ?ctype rdfs:label ?HistoryDisease.
  ?comv ADDO:hasValue "true"^^xsd:boolean.
  filter(((?mHistory= ADDO:smokingHistoryValue)||
  (?mHistory= ADDO:alcoholIntakeValue))&&
  ((?HistoryDisease="disorder of cardiac function")||
  (?HistoryDisease="disorder of coronary artery")))
```

Q12: Include all AD patients with moderate MMSE COG scores at a baseline visit and who have no family history of AD or dementia?

```
SELECT DISTINCT ?RID ?MMSE ?date WHERE {
  ?p ADDO:has_RID ?hRID;
  ADDO:has_patientProfile ?hprof.
  ?hprof ADDO:has_Visit ?hvisit.
  ?hvisit ADDO:Visit.Code ?hVcode;
  ADDO:has_diagnosis ?hdia;
  ADDO:has_CognitiveTest ?hcog.
  ?hdia ADDO:Diagnosis.value ?hdiav;
  ADDO:Diagnostic_Procedure.Date ?hdate.
  ?hcog ADDO:Diagnostic_Procedure.Value ?dvalue;
  rdf:type ?dt.
  ?dt rdfs:label
  "Mini_mental_status_examination"^^xsd:string.
  ?dvalue ADDO:hasValue ? MMSE.
  filter((?MMSE <=26) && (? MMSE >=21))
  ?hRID ADDO:hasValue ?RID.
  ?hVcode ADDO:hasValue "b1"^^xsd:string.
  ?hdiav ADDO:hasValue "AD"^^xsd:string.
  ?hdate ADDO:hasValue ?date.
  FILTER NOT EXISTS {?hprof ADDO:has_FamilyHistory ?FHis.
  ?FHis ADDO:Relative.FHQDAD ?AD;
  ADDO:Relative.FHQDADAD ?dementia.
  ?AD ADDO:hasValue "true"^^xsd:boolean.
  ?dementia ADDO:hasValue "true"^^xsd:boolean.}
  order by DESC(?date) ASC(?MMSE)
```

In this section, many competency questions are implemented in the SPARQL query. We have carefully selected these questions to cover many important clinical aspects of diagnosing AD. The SPARQL query answers were evaluated by the domain experts.

As a result, ADDO is understood clearly by the domain expert. It covered all medical concepts of AD. Their classes and properties are defined consistently. Finally, ADDO is a complete and accurate clinical knowledge of AD diagnosis.

V. ADDO FUZZY EXTENSION

ADDO ontology is a crisp ontology in which the membership degrees of all properties are equal to 1. So, it is limited to classifying precise information about AD. In contrast, most patient data is ambiguous and contains different ranges of linguistic values, especially diagnostic tests. For example, we reviewed some SPARQL queries in the previous section, such as Q2 required patients with low ADAS COG scores, and we used a crisp value of less than 15. Besides, Q12 required AD patients with moderate MMSE COG scores, and we used a crisp interval value [21], [26]. To avoid these problems, we have to extend ADDO to fuzzy ontology. Hopefully, our proposed model copes with vague values. It tries to solve inconsistency. It accommodates the linguistic variables that assist the fuzzy query formulation and enhance diagnosis results' efficiency.

In the fuzzy ontology domain, fuzzification is implemented using the fuzzy OWL 2 protégé's plugin in which Fuzzy aspects are formulated as annotations in the crisp ontology [51]. There are some requirements that must be taken into the crisp ontology, such as fuzzy logic annotation. ADDO uses Fuzzy logic to perform approximate reasoning. Fig. 8 shows a snapshot of the ADDO fuzzy logic annotation. Fuzzy data types are created for each of the ADDO Fuzzy terms. Fuzzy modifiers allow using real-world linguistic, such as very and slightly, in which fuzzy data types can get degrees of membership. Concepts are fuzzified, where the

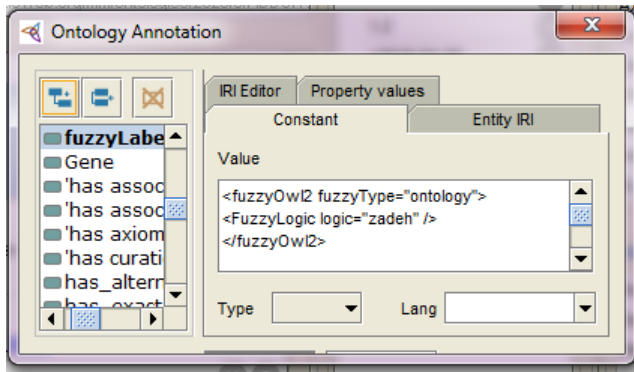


FIGURE 8. A snapshot of the ADDO fuzzy logic annotation.

instance belongs to a certain degree. Fuzzy role assertion connects instances at a membership degree.

Instance belongs to a Fuzzy concept in a certain membership degree. For example, ‘moderate_education’ (education_level) is a fuzzy concept, where ‘moderate’ is a linguistic term. Therefore, ‘moderate_education’ is a fuzzy concept, such as ‘RID_139 is an instance moderate_education at 0.9 membership degree’. An object property connects instances at a membership degree as ‘RID_1200 hasADASTest serve at a degree 0.7’. The property ‘hasADASTest’ connects instances ‘RID_1200’ and ‘serve’ at a degree of 0.7. Data property specifies a literal value to individuals at a certain degree, such as ‘RID_3_diagnosis_value has_value MCI at 0.8 membership degree’. Here, ‘has_value’ is a data property that connects instances ‘RID_3_diagnosis_value’ and ‘MCI’.

A. DEFINITION OF FUZZY SETS

ADD0 contains many diagnostic test categories, which are numerical features, such as cognitive tests, brain imaging parameters, and blood tests. For each of the numerical features, three Fuzzy types are defined, which are an abstract role, Fuzzy data type, and Fuzzy concrete role. We used the Fuzzy OWL plugin to define a Fuzzy data type for each Fuzzy value. This plugin contains four Fuzzy datatypes, such as leftshoulder, rightshoulder, trapezoidal, and triangular with k_1 , k_2 , a , b , c , and d parameters.

For instance, Mini-Mental State Examination (MMSE) [52] is useful for cognitive evaluation of the diagnosis and longitudinal assessment of AD. It is a 30-point questionnaire. It consists of various categories, like an orientation to time or place, recall, and language. Normal scores can indicate 28 points or more out of 30. Any score of 9 or less indicates a severe. Fig. 9 shows Fuzzy data type representation for MMSE. Fuzzy types are defined as follows.

- 1) Create an abstract role named MMSE.
- 2) Define a Fuzzy data type for each linguistic term and annotated it as a fuzzy datatype. MMSE range is [0.0, 30.0]. linguistic terms are
 SevereMMSE (leftshoulder (9, 10),
 ModerateMMSE (Trapezoidal (9, 10, 18, 19)),
 MildMMSE (Trapezoidal (18, 19, 24, 25)),
 MCIMMSE (Trapezoidal (24, 25, 27, 28)),

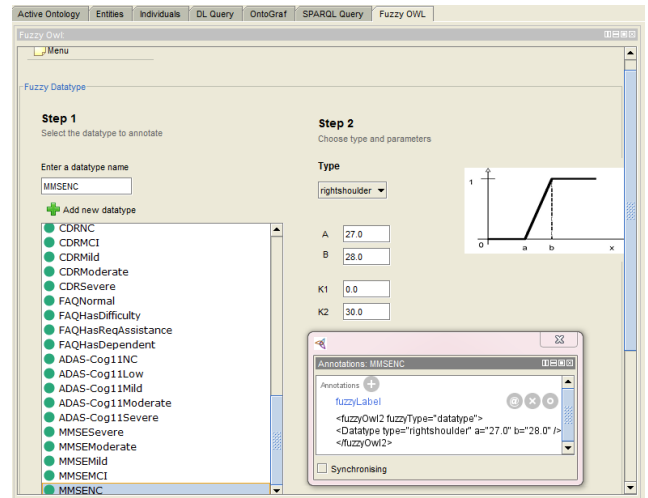


FIGURE 9. A snapshot of some ADD0 fuzzy data types.

- NormalMMSE (Rightshoulder (27, 28)).
- 3) Define fuzzy concrete roles for each linguistic term: hasSevereMMSE, hasModerateMMSE, hasMildMMSE, hasMCIMMSE, and hasNormalMMSE.
 hasSevereMMSE modeled as hasSevereMMSE (MMSE, SevereMMSE) where MMSE is a crisp concept and SevereMMSE is a fuzzy data type.

To discover behavioral changes and assess the patient’s mood, the original Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [53] includes 11 tasks (70-point). It consists of some questions like following commands, naming fingers and objects, and a word recognition task. Normal scores can refer to 12 or less, for more than 20 point estimate AD.

Several key brain regions volumes, including Ventricles, Hippocampus, WholeBrain, Entorhinal, Fusiform, and MidTemp, are susceptible to the pathophysiological changes correlating with AD [54]. For instance, the fuzzy data type representation for the Entorhinal and Hippocampus as follows:

- Entorhinal:
 Low (Trapezoidal (0 0 1608 3082)),
 Medium (Triangular (1608 3876 6144)),
 High (Trapezoidal (4670 6144 6938 8752)).
 Hippocampus :
 Low (Trapezoidal (0 0 3118 5456)),
 Medium (Triangular (3118 6715 1.031e+04)),
 High (Trapezoidal (47973 1.031e+04 1.157e+041.445e+04)).

Higher glucose levels [55] is a risk factor for AD. So, it’s a critical blood test. ADD0 contains five Fuzzy sets for blood glucose range from 0 to 300 milligrams per deciliter. Low scores equal to 45.0 or less, for more than 180 point estimate severe.

MATLAB is used to fuzzify all numerical features with the help of AD clinical guidelines. The designed Membership Functions (MFs) for each input variable of MMSE, ADAS-Cog11, blood sugar, and patient’s risk factor are shown in Figs. 10, 11, and 12, respectively. For more Fuzzy sets and their MFs, parameters of different variables have been shown in Table 6.

TABLE 6. A list of some linguistic variables, linguistic terms, and MFs.

Risk factor	Data type	Linguistic terms	MF shape	MF range	MF fuzzy parameters
Age (years)	Numerical	Very Young	Trapezoidal	$[\leq 20]$	(0, 0, 16, 20)
		Young	Triangular	$[18-38]$	(18, 28, 38)
		Mild	Triangular	$[35-55]$	(35, 45, 55)
		Old	Triangular	$[45-70]$	(45, 52, 70)
		Very Old	Trapezoidal	$[\geq 65]$	(65, 70, 100, 100)
Education(years)	Numerical	Low	Trapezoidal	$[\leq 10]$	(0, 0, 6, 10)
		Normal	Triangular	$[6-12]$	(6, 10, 12)
		High	Trapezoidal	$[\geq 10]$	(10, 12, 30, 30)
Systolic blood pressure (mmHg)	Numerical	Low	Trapezoidal	$[\leq 134]$	(0, 0, 100, 134)
		Normal	Triangular	$[127-153]$	(127, 134, 153)
		High	Triangular	$[142-172]$	(142, 153, 172)
		Very High	Trapezoidal	$[\geq 154]$	(154, 172, 180, 180)
Diastolic blood pressure (mmHg)	Numerical	Low	Trapezoidal	$[\leq 70]$	(0, 0, 50, 70)
		Normal	Triangular	$[50-110]$	(50, 70, 110)
		High	Trapezoidal	$[\geq 90]$	(90, 110, 120, 120)
Height(cm)	Numerical	Low	Trapezoidal	$[\leq 170]$	(0, 0, 160, 170)
		Normal	Triangular	$[160-180]$	(160, 170, 180)
		High	Trapezoidal	$[\geq 170]$	(170, 180, 250, 250)
Seated Pulse Rate (bpm)	Numerical	Low	Trapezoidal	$[\leq 80]$	(0, 0, 75, 80)
		Normal	Trapezoidal	$[75-136]$	(75, 80, 128, 136)
		High	Trapezoidal	$[\geq 75]$	(128, 136, 170, 170)
Red cell count	Numerical	Low	Trapezoidal	$[\leq 4.8]$	(0, 0, 4.2, 4.8)
		Normal	Triangular	$[4.2-5.4]$	(4.2, 4.8, 5.4)
		High	Trapezoidal	$[\geq 4.8]$	(4.8, 5.4, 6, 6)
Hbg (g/dL)	Numerical	Low	Trapezoidal	$[\leq 13.5]$	(0, 0, 11, 13.5)
		Normal	Triangular	$[11-16]$	(11, 13.5, 16)
		High	Trapezoidal	$[\geq 13.5]$	(13.5, 16, 20, 20)
White cell count	Numerical	Low	Trapezoidal	$[\leq 7.5]$	(0, 0, 4, 7.5)
		Normal	Triangular	$[4-11]$	(4, 7.5, 11)
		High	Trapezoidal	$[\geq 7.5]$	(7.5, 11, 15, 15)
Vitamin B12(ng/L)	Numerical	Low	Trapezoidal	$[\leq 100]$	(0, 0, 90, 100)
		Mild	Trapezoidal	$[100-200]$	(90, 100, 200, 220)
		Normal	Trapezoidal	$[\geq 200]$	(200, 220, 1000, 1000)
CDR	Numerical	NC	Trapezoidal	$[\leq 0.5]$	(0, 0, 0.3, 0.5)
		MCI	Triangular	$[0.5, 1]$	(0, 0.5, 1)
		Mild	Triangular	$[1, 2]$	(0.5, 1, 2)
		Moderate	Triangular	$[2, 3]$	(1, 2, 3)
		Severe	Trapezoidal	$[\geq 3]$	(2, 3, 3.7, 5)
FAQ	Numerical	Normal	Trapezoidal	$[\leq 2]$	(0, 0, 2, 10)
		Has Difficulty	Triangular	$[0, 20]$	(0, 10, 20)
		Req Assistance	Triangular	$[10, 30]$	(10, 20, 30)
		Dependent	Trapezoidal	$[\geq 28]$	(20, 28, 30, 30)
Ventricles	Numerical	Low	Trapezoidal	$[\leq 2.15e+04]$	(0 0 2.15e+04 6.44e+04)
		Medium	Triangular	$[6.44e+04 1.106e+05]$	(2.15e+04 8.75e+04 1.536e+05)
		High	Trapezoidal	$[\geq 1.536e+05]$	(1.106e+05 1.536e+05 1.766e+05 2.294e+05)
Fusiform	Numerical	Low	Trapezoidal	$[\leq 9960]$	(0 0 9960 1.573e+04)
		Medium	Triangular	$[1.573e+04 2.21e+04]$	(9.96e+03 1.89e+04 2.77e+04)
		High	Trapezoidal	$[\geq 2.78e+04]$	(2.21e+04 2.78e+04 3.1e+04 3.81e+04)
WholeBrain	Numerical	Low	Trapezoidal	$[\leq 7.328e+05]$	(0 0 7.328e+05 9.5e+05)
		Medium	Triangular	$[9.5e+05 1.19e+06]$	(7.328e+05 1.068e+06 1.402e+06)
		High	Trapezoidal	$[\geq 1.402e+06]$	(1.19e+06 1.402e+06 1.52e+06 1.79e+06)
Gender	Categorical	Male	Singleton	1	
		Female	Singleton	2	
Symptoms including fever, dizziness , catatonia, fatigue, etc	Ordinal	Normal	Triangular	$[0-0.4]$	(0, 0.2, 0.4)
		low	Triangular	$[0.2-0.6]$	(0.2, 0.4, 0.6)
		medium	Triangular	$[0.4-0.8]$	(0.4, 0.6, 0.8)
		high	Triangular	$[0.6-1]$	(0.6, 0.8, 1)
Diseases	Ordinal	Absent	Triangular	$[0-0.4]$	(0, 0.2, 0.4)
		Mild	Triangular	$[0.2-0.6]$	(0.2, 0.4, 0.6)
		Moderate	Triangular	$[0.4-0.8]$	(0.4, 0.6, 0.8)
		Sever	Triangular	$[0.6-1]$	(0.6, 0.8, 1)

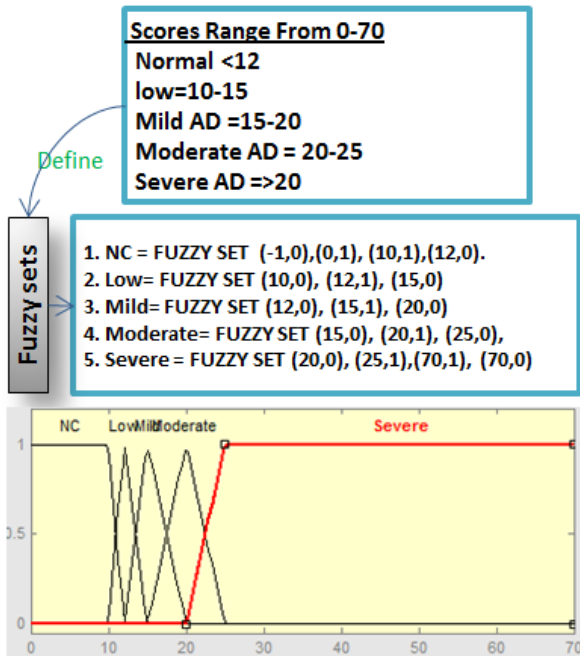


FIGURE 10. The fuzzy sets and MFs for ADAS-Cog11.

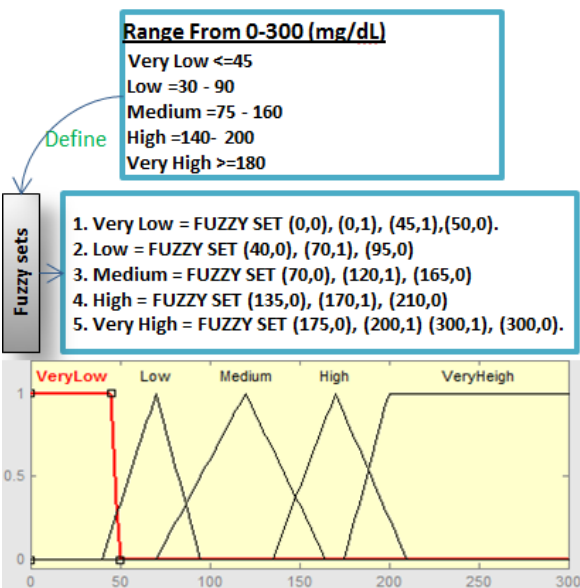


FIGURE 11. The fuzzy sets and MFs for blood glucose.

B. DEFINITION OF FUZZY MODIFIERS

Certainly, using fuzzy modifier values, such as very, little, slightly, and recently, to describe the Fuzzy concepts can improve semantic queries in the ontology. For example, the Fuzzy ADDO could be more expressive by adding the Fuzzy modifier ‘very,’ making it easier to get an axiom.

.EhasSevereMMSE.(very)SevereMMSE.

ADDO defined Fuzzy datatypes (SevereMMSE and Very-SevereMMSE) and Fuzzy modifier ‘Very’ by adding the following annotation:

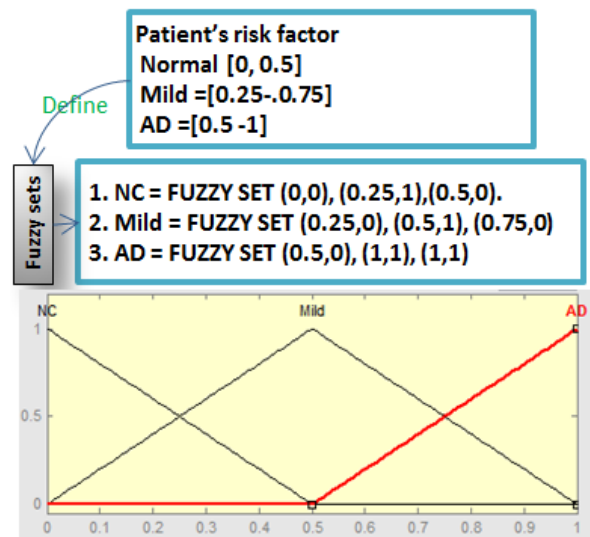


FIGURE 12. The fuzzy sets and MFs for patient's risk factor.

- Fuzzy datatypes SevereMMSE annotation

```
<fuzzyOwl2~fuzzyType="datatype">
<Datatype type="leftshoulder" a="9.0" b="10.0" />
</fuzzyOwl2>
```

- Fuzzy modifier very annotation

```
<fuzzyOwl2~fuzzyType="modifier">
<Modifier type="linear" c="0.8" />
</fuzzyOwl2>
```

- Fuzzy datatypes VerySevereMMSE annotation

```
<fuzzyOwl2~fuzzyType="datatype">
<Datatype type="modified" modifier="Very" base="
SevereMMSE" />
</fuzzyOwl2>
```

Fuzzy ADDO supports fuzzy modified roles by adding new roles., such as we can define Mild (Diagnosis.severity) or Moderate (Diagnosis.severity). The annotation of the Fuzzy modified Mild and the Fuzzy roles MildDiagnosis.severity as follows:

- Fuzzy modifier Mild annotation

```
<fuzzyOwl2~fuzzyType="modifier">
<Modifier type="linear" c="0.4" />
</fuzzyOwl2>
```

- Fuzzy modified roles MildDiagnosis.severity annotation

```
<fuzzyOwl2~fuzzyType="role">
<Role type="modified" modifier="Mild"
base="Diagnosis.severity" />
</fuzzyOwl2>
```

C. ADDO INSTANCES (ABOX)

The ADDO instances have been collected from ADNI CSV files as a case study. We have created a Fuzzy database for the Fuzzy ADDO ontology and filled it with 30 cases of NC, MCI, and AD patients to be store in the same ontology structure. Fig. 13 shows a fragment of the AD patient instances in the Fuzzy data set related to brain region volumes, Cerebrospinalfluid test, and cognitive test. The mapping

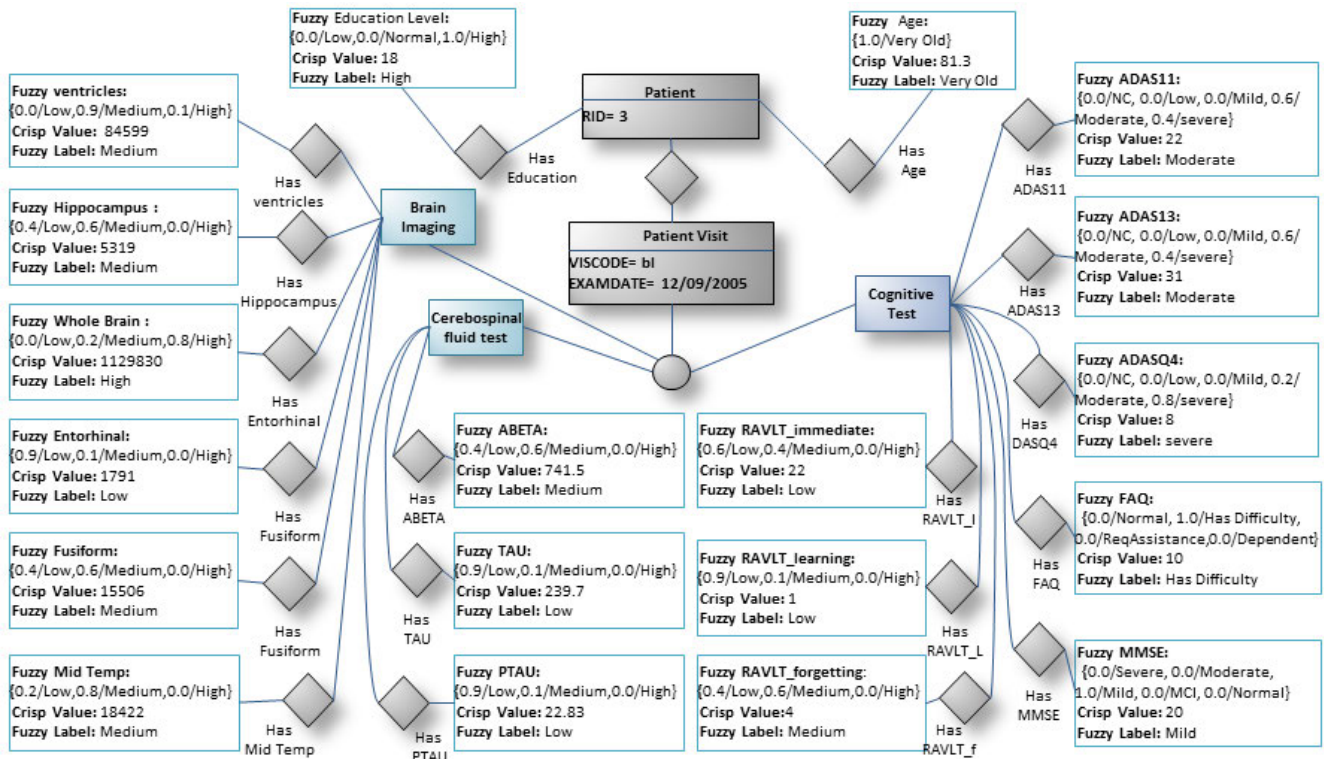


FIGURE 13. A fragment of the AD Patient instances in the fuzzy dataset related to brain regions volumes, cerebrospinal fluid test, and cognitive test.

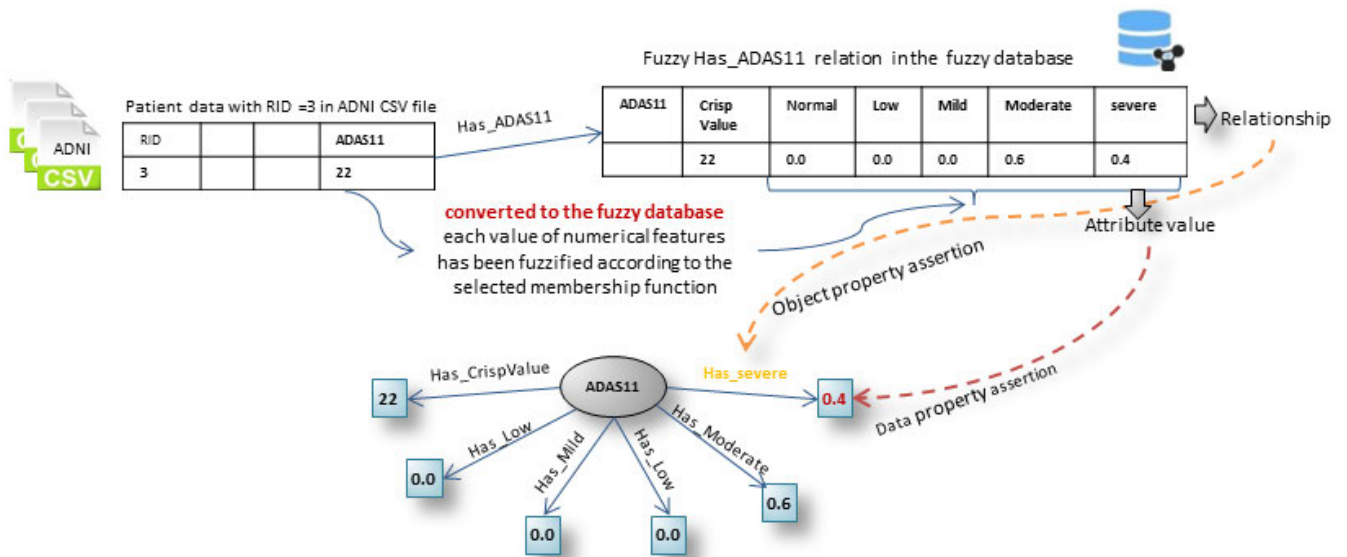


FIGURE 14. The mapping process between the fuzzy database and ADDO.

process between the Fuzzy database and ADDO is shown in Fig. 14. Each fuzzy object stored in our fuzzy database mapped to ADDO individual identifier and many properties (object property assertion and ADDO data property assertion) that implemented to ADDO by asserting some axioms. Data property assertion for the patient case illustrated in Fig. 14 is defined as follows:

```
<fuzzyOw12~fuzzyType="concept">
<Concept type="nominal" value="0.4"
individual="patient_3_ADAS11_severe" />
</fuzzyOw12>
```

```
<fuzzyOw12~fuzzyType="concept">
<Concept type="nominal" value="0.6"
individual="patient_3_ADAS11_Moderate" />
</fuzzyOw12>
```

D. QUERYING THE FUZZY ADDO

We designed many queries to ensure the efficiency of retrieving the instances.

Q1: Extract the patient RID with very old age, where MMSE test scores are severe along with severe ADAS-Cog11 score?

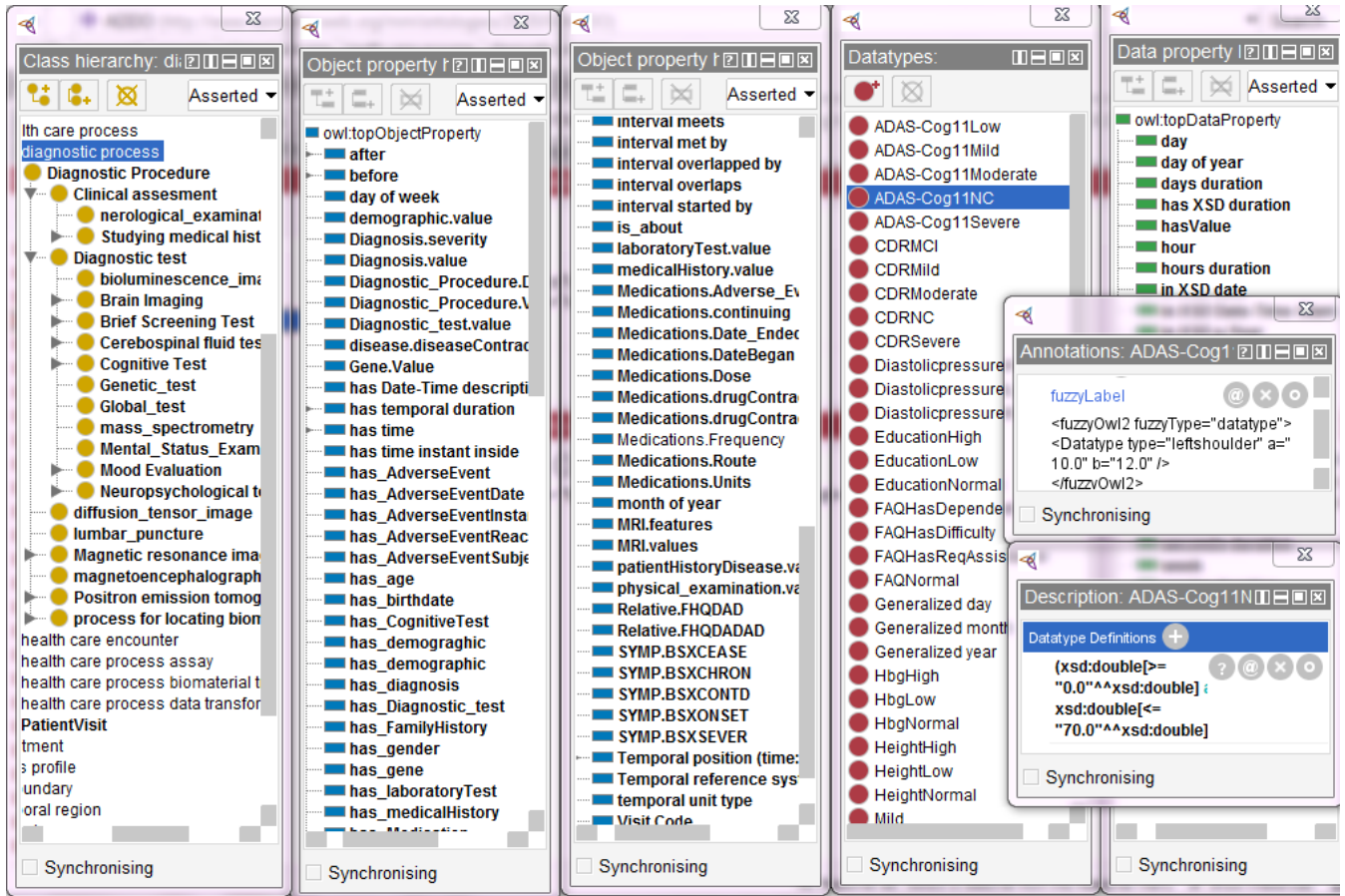


FIGURE 15. The Fuzzy ADDO classes, objects, fuzzy data types, and data properties.

```
has_age only (Age.value only (hasValue value VeryOld ))
and has_MMSETest some (MMSET.value some (hasValue
value MMSESevere)) and has_ADAS-Cog11~some (ADAS-Cog11.
value some (hasValue value ADAS-Cog11Severe)) and Patient
```

Q2: Find the drugs for an MCI patient whose HIV test is negative and whose blood sugar is very high?

```
Has_BloodSugar some (BloodSugar.value some
(hasValue value BloodSugar veryHigh)) and
Has_HIV some (HIV.value some (hasValue value
HIVpositive)) and medication
```

The Human Immunodeficiency Viruses (HIV) [56] may increase neurodegenerative disorders, such as AD. It is done due to neuronal damage from toxic viral products. The ontology used negative and BloodSugarVHigh as linguistic terms of the Fuzzy variable HIV test and blood sugar and extract the needed information.

VI. EXPERIMENT AND RESULTS

We introduced a methodology to develop Fuzzy semantic knowledge for decision-making. It is expected to be good practice in AD diagnosis to solve the linguistic variables and reasoning problems. Protégé was used to build semantic knowledge for decision-making. Fuzzy ADDO classes, objects, fuzzy data types, and data properties are shown in Fig. 15. The extended Fuzzy ADDO uses OWL2 and Fuzzy

annotation properties. The FuzzyOWL2 plug-in enables defining fuzzy elements to the ADDO ontology and uses fuzzyDL to reason query. The fuzzy ADDO evaluation process is based on two phases: ontology evaluation and a comparison between ADDO and other existing AD ontologies.

A. FUZZY ADDO EVALUATION

ADDO evaluation is an important and essential final step to measure the ontology’s performance and define the instances that might not be identical. In general, ontology evaluation is done based on two steps. The first one is running reasoners, such as Pellet and Hermit. The second step is the query execution in questions that required answers, such as the SPARQL and DL queries, to extract the required individuals or instances. The Hermit reasoner was used to evaluate ADDO.

B. COMPARISON WITH EXISTING AD ONTOLOGIES

Regarding existing AD studies, it is a lack of building a complete ontology model for AD patients as many of these systems rely on a limited number of concept categories in their knowledge as Ontology-Driven Decision, ADMO, OntoAD. Also, some ontologies have not been encoded with standard

TABLE 7. A comparison between ADDO and some existing AD ontologies.

	SWAN [20]	MIND [28]	ND [24]	Ontology Driven Decision [29]	OntoNeuro LOG [26]	ADO [27]	Multiagent [31]	AlzFuzzy Onto [30]	ADMO [23]	ADDO
Purpose	Knowledge inference	AD diagnosis	Terms standardization	AD diagnosis	Knowledge inference	Knowledge inference	remote monitoring	AD diagnosis	Pathophysiology	AD diagnosis
Based on a unified top-level ontology	No	No	Yes	No	No	Yes	No	No	Yes	Yes
Available for reuse	No	No	No	No	Yes	Yes	No	No	Yes	Future work
Supports interoperability with EHR	No	No	No	Yes	Yes	No	No	No	No	Yes
Has whole patient profile	No	Limited	No	No	No	No	No	Limited	No	Yes
Reuses existing ontologies	No	Yes	Yes	No	Yes	No	No	No	No	Yes
Contain fuzzy aspects	No	No	No	No	No	No	No	Yes	No	Yes
Last update	2009	2011	2012	2013	2013	2013	2015	2015	2018	2020

medical terminologies, not recognized as top-level ontology. ADO, MIND, and AlzFuzzyOnto have not supported the reusing of already existed ontologies. Furthermore, some ontologies' experimentation and instantiation have not been carried out, like CADRO and AlzFuzzyOnto. For publicly available, such as ontology SWAN, Multiagent, AlzFuzzyOnto, and Ontology-Driven Decision, are not publicly available. Such ontology does not provide a real and efficient AD diagnosis. They do not incorporate the other chronic diseases and symptoms of age-related changes besides AD that may affect the doctors' judgment.

Our proposed ADDO is fully developed as an extension of BFO and OGMS. ADDO supports AD clinical diagnosis and offers their risk level (NC, MCI, AD) based on representing the critical aspects of patients including disease, complications, medical history, physical examination, drug, symptoms, lab examination, MRI, and genes are considered. Finally, ADDO is extended to a fuzzy ontology, which makes it able to pass the difficulties of dealing with vague and medical linguistic terms. Table 7 shows A comparison between ADDO and other AD ontologies.

VII. CONCLUSION

AD is characterized as a chronic degenerative disease that involves a group of neurological disorders resulting from the accumulation of amyloid plaques that appear in the brain, affecting essential body functions. In this study, ADDO is developed as a standard fuzzy ontology-based semantic knowledge that aims to provide a warning to high-risk patients who have a high chance of having AD. A detailed analysis of patients and a timeline of patient visits is efficiently considered, including patient's demographic data, medical history, disease history, complications, medication, and covers many diagnostic tests. ADDO supports the

interoperability by adhering to BFO and OGMS top-level ontologies. Hopefully, ADDO has greater significance in the AD clinical environment. From the experimental results, ADDO provides a standard ontology and supports interoperability by integrating ADDO and heterogeneous AD data. We used ADNI to mapping a set of real instances. ADDO is evaluated by answering many SPARQL semantic queries. As an evaluation result, ADDO is consistent and reliable. In the future, ADDO will evolve to include rule-based implementation using SWRL rules to build rule-based reasoning for AD diagnosis. With the deterioration of the cases of Alzheimer's patients and their confinement to bed with the progress of the disease. Many cases remain with their relatives at home. We expect to make many additions as provides remote healthcare to AD patients with the help of their caregivers to monitor the progression of patients' disease. To help physicians automatically retrieve patient data required for diagnoses and improve accuracy hospitalized not only patients but also remote available patients.

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